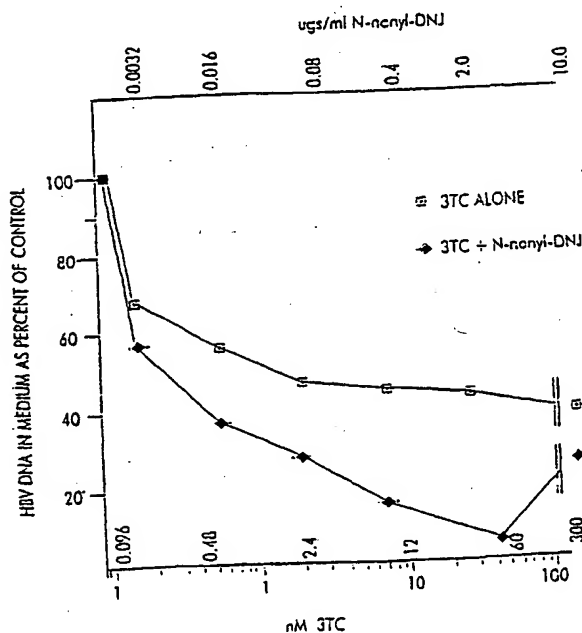




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(71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).			
(72) Inventors; and (75) Inventors/Applicants (for US only): MUELLER, Richard, A. [US/US]; 562 Stonegate Terrace, Glencoe, IL 60022 (US). BRYANT, Martin, L. [US/US]; 65 Hickory Lane, Carlisle, MA 01741 (US). PARTIS, Richard, A. [US/US]; 2221 Noyes Street, Evanston, IL 60201 (US).			
(74) Agents: ROEDEL, John, K., Jr.; Senniger, Powers, Leavitt & Roedel, One Metropolitan Square, 16th floor, St. Louis, MO 63102 (US) et al.		Published Without international search report and to be republished upon receipt of that report.	

(54) Title: USE OF SUBSTITUTED-1,5-DIDEOXY-1,5-IMINO-D-GLUCITOL COMPOUNDS FOR TREATING HEPATITIS VIRUS INFECTIONS



## (57) Abstract

N-Substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds of Formula (I) are effective in treatment of hepatitis infections, including hepatitis B and hepatitis C. In treating hepatitis infections, the compounds of Formula (I) may be used alone, or in combination with another antiviral agent selected from among nucleosides, nucleotides, immunomodulators, immunostimulants or various combinations of such other agents.

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USE OF SUBSTITUTED-1,5-DIDEOXY-1,5-IMINO-D-GLUCITOL  
COMPOUNDS FOR TREATING HEPATITIS VIRUS INFECTIONS

BACKGROUND OF THE INVENTION

5 Field of the Invention

The present invention relates to methods and compositions for treating hepatitis virus infections, especially hepatitis virus infections, particularly hepatitis B and hepatitis C, in mammals, especially humans. The methods comprise administering substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds alone or in combination with nucleoside antiviral agents, nucleotide antiviral agents, mixtures thereof, or, alternatively, in combination with immunomodulating/-immunostimulating agents. Administration of substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds in combination with both a nucleoside and/or nucleotide type antiviral agent and an immunomodulating/immunostimulating agent or agents is also contemplated. Combinations of anti-hepatitis viral agents show unexpected efficacy in inhibiting replication and secretion of hepatitis viruses in cells of mammals infected with these viruses.

Background of Invention

Over half the biologically important proteins are glycosylated and that glycosylation may vary with disease. Based upon this information, the use of drugs to control glycosylation patterns, glycoforms, changes or rates of change will have a biochemical effect, and may provide a beneficial therapeutic result. Control of glycolipid and glycoprotein sugar patterns as well as their synthesis and degradation leads to basic physiological effects on mammals including humans, agricultural animals and pets. Possibly, this is through influences on, for example, N-linked glycans, O-linked glycans, glucosaminoglycans, glycosphingolipids, glycosphospholipids, lectins, immuneoglobulin molecules, antibodies, glycoproteins and

their biochemical intermediates or conversion products. Modification of glycosylation site occupancy influences receptor and enzyme binding site specificity, selectivity, capacity, protein folding, enzyme activity, kinetics and energetics. Glycosidase and glycosyltransferase systems are two biochemical mechanisms that are suggested to affect such systems (Dwek, Raymond A., *Glycobiology: Toward Understanding the Function of Sugars*, Chemical Reviews, 96, 683-720 (1996)).

Other hepatitis viruses significant as agents of human disease include Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis Delta, Hepatitis E, Hepatitis F, and Hepatitis G (Coates, J. A. V., et.al., *Exp. Opin. Ther. Patents* (1995) 5(8):747-756). Hepatitis C infection is also on the increase and effective treatments are needed. In addition, there are animal hepatitis viruses that are species-specific, but serves as excellent models for the human disease. These include, for example, those infecting ducks, woodchucks, cattle and mice.

#### 1,5-dideoxy-1,5-imino-D-glucitol Compounds

1,5-dideoxy-1,5-imino-D-glucitol (also known as 1-deoxynojirimycin, DNJ) and its *N*-alkyl derivatives (together, "imino sugars") are known inhibitors of the *N*-linked oligosaccharide processing enzymes alpha glucosidase I and II (Saunier et al., *J. Biol.Chem.* (1982) 257:14155-14161 (1982); Elbein, *Ann. Rev. Biochem.* (1987) 56:497-534). As glucose analogs, they also have potential to inhibit glucose transport, glucosyl-transferases, and/or glycolipid synthesis (Newbrun et al., *Arch. Oral Biol.* (1983) 28: 516-536; Wang et al., *Tetrahedron Lett.* (1993) 34:403-406). Their inhibitory activity against glucosidases has led to the development of these compounds as anti-hyperglycemic agents and antiviral agents. See, for example, PCT International Publication WO 87/03903 and U.S. Patents



4,065,562; 4,182,767; 4,533,668; 4,639,436; 4,849,430;  
4,957,926; 5,011,829; and 5,030,638.

Glucosidase inhibitors such as N-alkyl-1,5-dideoxy-1,5-imino-D-glucitol compounds wherein the alkyl group contains  
5 between three and six carbon atoms have been shown to be effective in the treatment of Hepatitis B infection (PCT International Publication WO 95/19172). For example, N-(n-butyl)-deoxynojirimycin (N-butyl-DNJ; N-(n-butyl)-1-5-dideoxy-1,5-imino-D-glucitol) is effective for this purpose  
10 (Block, T. M., *Proc. Natl. Acad. Sci. USA* (1994) 91:2235-2239; Ganem, B. *Chemtracts: Organic Chemistry* (1994) 7(2), 106-107). N-butyl-DNJ has also been tested as an anti-HIV-1 agent in HIV infected patients, and is known to be well tolerated. Another alpha glucosidase inhibitor,  
15 deoxynojirimycin (DNJ), has been suggested as an antiviral agent for use in combination with N-(phosphonoacetyl)-L-aspartic acid (PALA) (WO 93/18763). However, combinations of N-substituted-imino-D-glucitol derivatives and other antiviral agents for the treatment of hepatitis virus  
20 infections have not been previously disclosed or suggested. From results obtained in a woodchuck animal model of hepatitis virus infection, Block et al. ((1998) *Nature Medicine* 4(5):610-614) suggested that glucosidase inhibitors such as N-nonyl DNJ, which interfere with specific steps in  
25 the N-linked glycosylation pathway of hepatitis virus glycoproteins, may be useful in targeting glycosylation processing as a therapeutic intervention for hepatitis B virus.

Compounds such as N-butyl-DNJ (N-butyl-  
30 deoxynojirimycin) and N-butyl-DGNJ (N-butyl-desoxynogalactonojirimycin) are reported as treatments of lysosomal storage diseases such as Tay-Sachs disease, Gauchers disease and related ailments. In addition, treatment of cholera has been reported (US 5,399,567) via  
35 inhibition of the synthesis of glycolipids (US 5,472,969). It has been reported that inhibition of glycosyl transferase

or glycosidase enzymes affects the catabolism and metabolism of phospholipids, sphingolipids, cerebrosides, gangliosides by or and within mammalian cells or interferes with such biochemical processes as attachment to cells, penetration of cells and/or release from cells. In any event, treatments for these diseases are badly needed since "With rare exceptions a treatment of these often lethal diseases is not possible to date." (Kolter, T and Sandhoff, K, Inhibitors of Glycosphingolipid Biosynthesis, Chemical Society Reviews, 371-381 (1996), WO 98/02161.

The use of N-butyl-1,5-dideoxy-1,5-imino-D-glucose and certain other imino-glucose compounds for the treatment of diseases caused or induced by human immunodeficiency virus (HIV), cytomeglovirus CMV), hepatitis virus, respiratory syncytial virus (RSV) and herpes virus (HSV) infection has been reported.

#### Nucleoside and Nucleotide Antiviral Agents

Reverse transcriptase inhibitors, including the class of nucleoside and nucleotide analogs, were first developed as drugs for the treatment of retroviruses such as human immunodeficiency virus (HIV), the causative agent of AIDS. Increasingly, these compounds have found use against other viruses, including both RNA and DNA viruses, via viral screening and chemical modification strategies. Nucleoside and nucleotide analogs exert their antiviral activities by inhibiting the corresponding DNA and RNA polymerases responsible for synthesis of viral DNA and RNA, respectively. Because viruses contain different forms of polymerases, the same nucleoside/nucleotide compound can have a dramatically different effect against different viruses. For example, lamivudine (3TC) appears to be useful against HBV infection, whereas zidovudine (AZT) appears to have little use against the same virus (Gish, R.G., et al., Exp. Opin. Invest. Drugs (1995) 4(2):95-115).

AZT is an example of a nucleoside/nucleotide analog that can effect glycosylation processes at clinically achievable concentrations rather than interfere with DNA replication or protein synthesis (Yan, J., et al., J. Biol. Chem., 270, 22836 (1995)).

Toxicity has been significant with some nucleoside analog antivirals. For example, clinical tests on the use of the nucleoside analog fialuridine (FIAU) for treatment of chronic hepatitis B were suspended recently due to drug-related liver failure leading to death in some patients. Consequently, there is still a need for safer drug regimens for the treatment of hepatitis B infections and hepatitis (Mutchnick, M. G., et. al., Antiviral Research (1994) 24:245-257).

#### Immunomodulators and Immunostimulants

Immunomodulators/immunostimulators such as interferon alpha and other cytokines have been used for the treatment of HBV infection with promising results. Unfortunately, the response rates are lower than desired. Interferon treatment is currently approved by the FDA for the treatment of Hepatitis B. Other immune system-affecting drug candidates are presently being investigated. These include thymic peptides for use in the treatment of chronic hepatitis B (CHB), isoprinosine, steroids, Schiff base-forming salicylaldehyde derivatives such as Tucaresol, levamisol, and the like (Gish, R. G., et al., *Exp. Opin. Invest. Drugs* (1995) 4(2):95-115; Coates, J.A.V., et al., *Exp. Opin. Ther. Patents* (1995) 5(8):747-765).

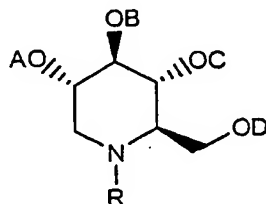
#### SUMMARY OF THE INVENTION

As noted above, the use of the substituted-imino-D-glucitol compounds and derivatives thereof disclosed herein alone, or in combination with other anti-hepatitis virus compounds has, to the present inventor's knowledge, neither been suggested nor disclosed. The use of two or more anti-

viral agents to provide improved therapy for the treatment of hepatitis B virus and hepatitis C virus infections is desirable due to the morbidity and mortality of the disease. Combination therapy is also desirable since it can reduce toxicity in patients as it enables the physician to administer lower doses of one or more of the drugs being given to a patient. Combination therapy can also help to prevent the development of drug resistance in patients (Wiltink, E. H. H., *Pharmaceutish Weekblads Scientific Edition* (1992) 14(4A):268-274). The result of an improved efficacy configuration combined with a relative lack of toxicity and development of resistance would provide a much improved drug treatment profile.

Substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds disclosed herein are effective in treating hepatitis virus infections. The use of these compounds in combination with nucleoside or nucleotide antiviral compounds, or combinations thereof, and/or immunomodulators/immunostimulants, is especially effective against hepatitis viruses.

Accordingly, in a first aspect, the present invention provides a method of treating a hepatitis virus infection in a mammal, comprising administering to said mammal an anti-hepatitis virus effective amount of at least one substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof:



Formula I

R is alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, cycloalkenylalkyl, cycloalkenylalkenyl, cycloalkenylalkynyl, bicycloalkenylalkyl, tricycloalkenylalkyl,

tetracycloalkenylalkyl, bicycloalkenoxyalkyl,  
 tricycloalkenoxyalkyl, tetracycloalkenyloxyalkyl,  
 cycloalkylalkenyl, cycloalkylalkynyl, aralkenyl, aralkynyl,  
 substituted aralkyl, aralkoxyalkyl, aralkoxyalkenyl,  
 5 aralkoxyalkynyl, aralkenoxyalkyl, aralkenoxyalkenyl,  
 heteroarylalkyl, heterocyclooxyalkyl, heterocycloethiaalkyl,  
 heterocycloalkenyl, heteroarylakenyl, heteroarylalkynyl,  
 aryloxyalkyl, aryloxyalkenyl, aryloxyalkynyl, haloalkyl,  
 hydroxyalkyl, dihydroxyalkyl, hydroxyalkenyl,  
 10 dihydroxyalkenyl, hydroxyalkynyl, haloalkyloxyalkyl,  
 haloalkoxyalkenyl, haloalkoxyalkynyl, carbonyl,  
 cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkylcarbonyl,  
 alkenylcarbonyl, alkynylcarbonyl, arylcarbonylalkyl,  
 arylalkylcarbonyl, arylalkenylcarbonyl,  
 15 arylalkyloxycarbonyl, aryloxyalkylcarbonyl,  
 haloalkylcarbonyl, hydroxyalkylcarbonyl,  
 haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl,  
 alkoxyalkylcarbonyl, alkyloxycarbonyl, alkanoyloxyalkyl,  
 aryloxyalkoxyalkyl, aryloxyalkyl, aminoalkyl,  
 20 alkanoylaminoalkyl, aminoalkyl, aminocarbonylalkyl,  
 hydroxysulfonealkyl, aminosulfonealkyl,  
 aminocarbonylaminoalkyl, aroylaminoalkyl,  
 alkoxycarbonylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl  
 or R<sup>5</sup>, wherein

25  $R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_pR^6$ - wherein:

R<sup>1</sup> is alkyl, aryl, alkenyl, alkynyl, hydrogen or  
 haloalkyl;

R<sup>2</sup> is alkylene, alkenylene, alkynylene or haloalkylene;

R<sup>3</sup> is alkylene, alkenylene, alkynylene or haloalkylene;

30 R<sup>4</sup> is alkylene, alkenylene, alkynylene or haloalkylene;

R<sup>6</sup> is alkylene, alkenylene, alkynylene, or  
 haloaldylene;

X<sup>1</sup> is independently oxygen, sulfur, sulfoxide or  
 sulfone;

35 X<sup>2</sup> is independently oxygen, sulfur, sulfoxide or  
 sulfone;

$X^3$  is independently oxygen, sulfur, sulfoxide or sulfone;

$X^4$  is independently oxygen, sulfur, sulfoxide or sulfone;

5         $m$ ,  $n$  and  $p$  are independently 0, 1, 2, or 3; and  
          $m + n + p \leq 3$

$A$ ,  $B$ ,  $C$ , and  $D$  are independently hydrido, lower alkyl, lowerhaloalkyl or acyl;

$D$  and  $R$  taken together may form a five or six membered  
10        ring when  $R$  is carbonyl or alkylcarbonyl;

$A$  and  $B$  taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

$B$  and  $C$  taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;  
15        and

$C$  and  $D$  taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

         wherein the main chain in  $R$  contains between one and twenty atoms; and

20        the main chain of  $R^5$  containing between four and twenty atoms.

         In a second aspect, the present invention provides a method for treating a hepatitis virus infection in a mammal, comprising administering to said mammal an antiviral  
25        composition consisting essentially of an antiviral effective amount of at least one substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I as defined above, or a pharmaceutically acceptable salt thereof.

         In a third aspect, the present invention provides a  
30        method for treating a hepatitis virus infection in a mammal, comprising administering to said mammal an antiviral composition containing an antiviral effective amount of at least one substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I, as defined above or a  
35        pharmaceutically acceptable salt thereof, as above, substantially exclusive of the administration of any

antiviral agent comprising a nucleoside, a nucleotide, an immunomodulator, or an immunostimulant.

In a fourth aspect, the present invention provides a method for treating a hepatitis virus infection in a mammal, consisting essentially of administering to said mammal an  
5 antiviral composition comprising an antiviral effective amount of at least one substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I, as defined above, or a pharmaceutically acceptable salt thereof, as above. In this  
10 method, the antiviral composition can consist essentially of an antiviral effective amount of the substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I, or a pharmaceutically acceptable salt thereof.

In a fifth aspect, the present invention provides a  
15 method of treating a hepatitis virus infection in a mammal, comprising administering to said mammal a first amount of at least one substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I, as defined above, or a pharmaceutically acceptable salt thereof and a second amount  
20 of an antiviral compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, an immunomodulator, an immunostimulant, and mixtures thereof, wherein said first and second amounts of said compounds together comprise an anti-hepatitis virus  
25 effective amount of said compounds.

In a sixth aspect the invention is directed to a method for treating a hepatitis virus infection in a mammal, consisting essentially of administering to said mammal an anti-hepatitis virus effective amount of an antiviral  
30 composition consisting essentially of at least one N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof.

In a seventh aspect, the invention is directed to a method consisting essentially of administering to said  
35 mammal an anti-hepatitis virus effective amount of a composition containing an anti-viral agent, said anti-viral

agent consisting essentially of at least one N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof.

5 In another aspect, the present invention provides a method of treating a hepatitis virus infection in a mammal, comprising administering to said mammal from about 0.1 mg/kg/day to about 100 mg/kg/day of at least one substituted-1,5-dideoxy-1,5-imino- D-glucitol compound of Formula I, as above, and from about 0.1 mg/person/day to  
10 about 500 mg/person/day of a compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and a mixture thereof.

In another aspect, the present invention provides a pharmaceutical composition, consisting essentially of an  
15 antiviral effective amount of at least one N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I, as defined above, or a pharmaceutically acceptable salt thereof, as above and a pharmaceutically acceptable carrier, excipient, or diluent.

20 In another aspect, the present invention provides a pharmaceutical composition, containing an antiviral effective amount of at least one substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof, as above,  
25 substantially exclusive of any antiviral agent comprising a nucleoside, a nucleotide, an immunomodulator, or an immunostimulant and a pharmaceutically acceptable carrier, diluent, or excipient.

In another aspect, the present invention provides a  
30 composition, comprising at least one substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I, as above, and an antiviral compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, an immunomodulator, an immunostimulant,  
35 and mixtures thereof.



In another aspect, the present invention provides a pharmaceutical composition, comprising a first amount of at least one substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I, as above, a second amount of an  
5 antiviral compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, an immunomodulator, and immunostimulant, and mixtures thereof, and a pharmaceutically acceptable carrier, diluent, or excipient, wherein said first and second amounts  
10 of said compounds together comprise an antiviral effective amount of said compounds.

In yet a further aspect, the present invention provides a pharmaceutical composition for treating a hepatitis B virus infection in a mammal, comprising from  
15 about 0.1 mg to about 100 mg of at least one substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I, as above, and from about 0.1 mg to about 500 mg of a compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral, and mixtures thereof, and  
20 a pharmaceutically acceptable carrier, diluent, or excipient.

Also provided is a pharmaceutical composition for treating a hepatitis virus infection in a human patient, comprising from about 0.1 mg to about 100 mg of (n-nonenyl)-  
25 1,5-dideoxy-1,5-imino-D-glucitol, from about 0.1 mg to about 500 mg of (-)-2'-deoxy-3'-thiocytidine-5'-triphosphate, and a pharmaceutically acceptable carrier, diluent, or excipient.

In another aspect, nucleosides and nucleotides and  
30 analogs such as AZT that inhibit sugar processing in addition to or instead of interfering with DNA or RNA are of special interest for use in combination therapy with iminosugars of this invention and for use in pharmaceutical formulations with the iminosugars disclosed herein. We  
35 intend that compounds such as AZT are useful in combination with the iminosugars disclosed herein for the treatment of

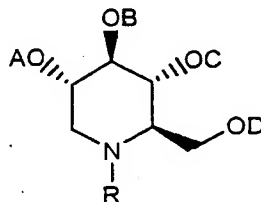
diseases described with regard to the various aspects of this invention.

Each of the methods of the invention as described hereinabove is effective for treating various forms of infectious hepatitis. Forms of hepatitis which can be treated by administration of the above-described imino sugars include hepatitis B, hepatitis C, hepatitis delta, hepatitis E, hepatitis F and hepatitis G. The methods of the invention, as detailed hereinbelow, are particularly suited and preferred for the treatment of hepatitis B and hepatitis C.

In another aspect, the present invention provides intermediates useful for the preparation of substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds or a salt thereof used alone or in combination in the treatment of Hepatitis B infection.

Also provided is a salt, comprising an anti-hepatitis effective amount of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I, as described above, and a nucleoside having an acidic moiety or a nucleotide.

Also provided is a compound, comprising an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound selected from:



R is aryloxyalkyl, monoalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxy-alkyl, alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, arylalkyloxycarbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, or  $R^5$ , wherein

$$R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_p \quad R^6- \text{ or hydrido};$$

$R^1$  is alkyl, aryl, alkenyl, alkynyl, hydrogen or haloalkyl;

$R^2$  is alkylene, alkenylene, alkynylene or haloalkylene;

$R^3$  is alkylene, alkenylene, alkynylene or haloalkylene;

$R^4$  is alkylene, alkenylene, alkynylene or haloalkylene;

$R^6$  is alkylene, alkenylene, alkynylene or haloalkylene;

$X^1$  is independently oxygen, sulfur, sulfoxide or sulfone;

$X^2$  is independently oxygen, sulfur, sulfoxide or sulfone;

$X^3$  is independently oxygen, sulfur, sulfoxide or sulfone;

$X^4$  is independently oxygen, sulfur, sulfoxide or sulfone;

$m$ ,  $n$  and  $p$  are independently 0, 1, 2, or 3;

$(m + n + p) \geq 3$ ; and

$(m + n + p) \geq 2$  and not all of  $R^2$ ,  $R^3$ , and  $R^4$  are alkylene when all of  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  are oxygen;

A, B, C, and D are independently hydrido, lower alkyl, lowerhaloalkyl or acyl;

A and B taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

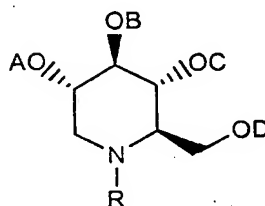
B and C taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

C and D taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

wherein the main chain in R contains between one and twenty atoms; and

the main chain of R<sup>5</sup> containing between four and twenty atoms.

Also provided is a chemical preparation intermediate selected from the group consisting of:



Formula I

R is alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, aryloxyalkyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, cycloalkylalkylcarbonyl, alkoxycarbonyl, alkylcarbonyl, aryloxyalkoxyalkylcarbonyl, alkylcarbonyloxyalkylcarbonyl, arylcarbonyloxyalkylcarbonyl, aminoalkylcarbonyl, alkylcarbonylaminoalkylcarbonyl, arylcarbonylaminoalkylcarbonyl, alkoxycarbonylaminoalkylcarbonyl, aminocarbonylaminoalkylcarbonyl, aminothiocarbonylaminoalkylcarbonyl, arylalkenylcarbonyl, carboxyalkylcarbonyl, alkoxycarbonylalkylcarbonyl, aminocarbonylalkylcarbonyl, aminothiocarbonylalkylcarbonyl, aminosulfonealkylcarbonyl, arylalkynylcarbonyl, heterocycloalkylcarbonyl, heteroarylalkylcarbonyl, heteroaryloxyalkylcarbonyl, heteroarylthiaalkylcarbonyl, heterocyclooxyalkylcarbonyl, heterocyclothiaalkylcarbonyl, arylthiaalkylcarbonyl, monohaloalkylcarbonyl,

haloalkyloxyalkylcarbonyl, cycloalkylalkyloxyalkylcarbonyl or  $R^5$ carbonyl wherein  $R^5$  is as defined hereinabove.

Further scope of the present invention will become apparent from the detailed description and drawings provided below. However, it should be understood that the following detailed description and examples, while indicating preferred embodiments of the invention, are given by way of illustration only since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

#### BRIEF DESCRIPTION OF THE DRAWINGS

The above and other objects, features, and advantages of the present invention will be better understood from the following detailed description taken in conjunction with the accompanying drawings, all of which are given by way of illustration only, and are not limitative of the present invention, in which:

Figure 1 shows the anti-hepatitis B virus activity of (-)-2'-deoxy-3'-thiocytidine-5'-triphosphate (3TC) alone and in combination with N-nonyl-DNJ in vitro.

Figure 2 shows the plasma concentration of N-nonyl-DNJ versus dose of N-nonyl-DNJ for each animal in Example 5, from samples taken during dosing. Animals are indicated by unique letters, and a small amount of random noise has been added to the dose value so that overlapping values can be distinguished.

Figure 3 shows the slope of  $\text{Log}(\text{IPDNA} + 10)$  to week versus dose. A distinct letter is used for each animal. The fitted line is from a four parameter logistic model. The parameters of the fitted curve and their approximate standard errors are shown on the plot.

DETAILED DESCRIPTION OF THE INVENTION

The following detailed description is provided to aid those skilled in the art in practicing the present invention. Even so, this detailed description should not be construed to unduly limit the present invention as modifications and variations in the embodiments discussed herein can be made by those of ordinary skill in the art without departing from the spirit or scope of the present inventive discovery.

The contents of each of the patent documents and other references cited herein, including the contents of the references cited within these primary references, are herein incorporated by reference in their entirety.

It has been discovered that the use of substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds is effective when such compounds are used alone for treating hepatitis virus infections. In accordance with the present invention, it has additionally been discovered that combinations of substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds with anti-hepatitis virus nucleosides or nucleotides, and/or immunomodulators/immunostimulants, are also effective for this purpose.

The present invention thus provides pharmaceutical compositions and methods of treating hepatitis virus infections, especially hepatitis B and C virus infections, in humans, other mammals, and cells using substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds alone or in combination with either an antiviral nucleoside, an antiviral nucleotide, mixtures thereof, and/or an immunomodulating or immunostimulating agent. The substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds may have basic nitrogen atoms and may be used in the form of a pharmaceutically acceptable salt. Nucleosides and nucleotides useful in the present invention are substituted purine or pyrimidine heterocycles further substituted with  $R^1$  in Formulas II-VI at the 9 position in the case of

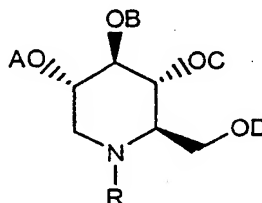
purines or with R<sup>1</sup> at the 1 position in the case of pyrimidines. The immunomodulating and immunostimulating agents useful in the present invention include those that stimulate immune responses effective in controlling or eliminating viruses or other infectious agents. Non-limiting examples of such immunomodulating and immunostimulating agents include cytokines, peptide agonists, steroids, and classic drugs such as tetramisole (levamisole). The drug combinations of this invention may be provided to a cell or cells, or to a human or other mammalian patient, either in separate pharmaceutically acceptable formulations administered simultaneously or sequentially, formulations containing more than one therapeutic agent, or by an assortment of single agent and multiple agent formulations. However administered, these drug combinations form an anti-hepatitis virus effective amount of components.

As used herein, the term "anti-hepatitis-virus effective amount" refers to an amount of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound that is effective when used alone in treating hepatitis virus infection, or a combined amount of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol and another antiviral agent that is effective in such treatment. The combined amounts of antiviral agent can be provided via combinations of: (1) an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound with either an antiviral nucleoside, an antiviral nucleotide, or a mixture of an antiviral nucleoside and an antiviral nucleotide; (2) an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound with an immunomodulating/-immunostimulating agent (or mixtures thereof), or (3) an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound with an antiviral nucleoside, an antiviral nucleotide, or a mixture thereof, plus an immunomodulating/-immunostimulating agent (or mixtures thereof). The antiviral effectiveness of the aforementioned combinations may involve a variety of different phenomena

associated with viral replication and assembly. These may include, for example, blocking hepatitis viral DNA synthesis; blocking viral transcription; blocking virion assembly; blocking virion release or secretion from infected cells; blocking or altering viral protein function, including the function of viral envelope protein(s); and/or the production of immature or otherwise non-functional virions. The overall effect is an inhibition of viral replication and infection of additional cells, and therefore inhibition of the progress of infection in the patient.

Substituted-1,5-dideoxy-1,5-imino-D-glucose compounds

Substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds useful in the present invention are represented by structure I below or salts thereof:



Formula I

R is alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, cycloalkenylalkyl, cycloalkenylalkenyl, cycloalkenylalkynyl, bicycloalkenylalkyl, tricycloalkenylalkyl, tetracycloalkenylalkyl, bicycloalkenoxyalkyl, tricycloalkenoxyalkyl, tetracycloalkenyloxyalkyl, cycloalkylalkenyl, cycloalkylalkynyl, aralkenyl, aralkynyl, substituted aralkyl, aralkoxyalkyl, aralkoxyalkenyl, aralkoxyalkynyl, aralkenoxyalkyl, aralkenoxyalkenyl, heteroarylalkyl, heterocyclooxyalkyl, heterocyclothiaalkyl, heterocycloalkenyl, heteroarylalkenyl, heteroarylalkynyl, aryloxyalkyl, aryloxyalkenyl, aryloxyalkynyl, haloalkyl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkenyl,



dihydroxyalkenyl, hydroxyalkynyl, haloalkyloxyalkyl,  
 haloalkoxyalkenyl, haloalkoxyalkynyl, carbonyl,  
 cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkylcarbonyl,  
 alkenylcarbonyl, alkynylcarbonyl, arylcarbonylalkyl,  
 5 arylalkylcarbonyl, arylalkenylcarbonyl,  
 substitutedarylalkylcarbonyl, arylalkyloxycarbonyl,  
 aryloxyalkylcarbonyl, haloalkylcarbonyl,  
 hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl,  
 cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl,  
 10 alkyloxycarbonyl, alkanoyloxyalkyl, aryloxyalkoxyalkyl,  
 aryloxyalkyl, aminoalkyl, alkanoylaminoalkyl,  
 aminocarbonylalkyl, hydroxysulfonealkyl, aminosulfonealkyl,  
 aminocarbonylaminoalkyl, aroylaminoalkyl,  
 alkoxycarbonylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl  
 15 or R<sup>5</sup>, wherein

$R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_pR^6-$  wherein:

R<sup>1</sup> is alkyl, aryl, alkenyl, alkynyl, hydrogen or  
 haloalkyl;

R<sup>2</sup> is alkylene, alkenylene, alkynylene or haloalkylene;

20 R<sup>3</sup> is alkylene, alkenylene, alkynylene or haloalkylene;

R<sup>4</sup> is alkylene, alkenylene, alkynylene or haloalkylene;

R<sup>6</sup> is alkylene, alkenylene, alkynylene, or  
 haloalkylene;

25 X<sup>1</sup> is independently oxygen, sulfur, sulfoxide or  
 sulfone;

X<sup>2</sup> is independently oxygen, sulfur, sulfoxide or  
 sulfone;

X<sup>3</sup> is independently oxygen, sulfur, sulfoxide or  
 sulfone;

30 X<sup>4</sup> is independently oxygen, sulfur, sulfoxide or  
 sulfone;

m, n and p are independently 0, 1, 2, or 3; and

$m + n + p \leq 3$

35 A, B, C, and D are independently hydrido, lower alkyl,  
 lowerhaloalkyl or acyl;

D and R taken together may form a five or six membered ring when R is carbonyl or alkylcarbonyl;

A and B taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

5        B and C taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring; and

C and D taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

10        wherein the main chain in R contains between one and twenty atoms; and

the main chain of R<sup>5</sup> containing between four and twenty atoms.

15        As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to and including 20 carbon atoms. Substituted alkyl, alone or in combination, means an alkyl radical which is optionally substituted as defined herein with respect to the definitions of aryl and heterocyclo.

20        Alkylene means a saturated aliphatic hydrocarbon moiety attached at two or more positions such as methylene (-CH<sub>2</sub>-). Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like.

25        The term "lower alkyl", alone or in combination, means alkyl containing from 1 to and including 6 carbon atoms.

30        The phrase "in the main chain" means the longest contiguous or adjacent chain of carbon atoms starting at the point of attachment of a group to the compounds of this invention.

The phrase "linear chain of atoms" means the longest straight chain of atoms independently selected from carbon, nitrogen, oxygen and sulfur.

35        The term "hydrido" means a hydrogen substituent, i.e., -H.

The term "alkenyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20 carbon atoms. Substituted alkenyl, alone or in combination, means an alkyl radical which is optionally substituted as defined herein with respect to the definitions of aryl and heterocyclo. Alkenylene means a carbon-carbon double bond system attached at two or more positions such as ethenylene (-CH=CH-). Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like.

The term lower "alkenyl", alone or in combination, means alkenyl containing from 2 to and including 6 carbon atoms.

The term "alkynyl", alone or in combination, means a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing preferably from 2 to 20 carbon atoms. Substituted alkynyl, alone or in combination, means an alkyl radical which is optionally substituted as defined herein with respect to the definitions of aryl and heterocyclo. Alkynylene means a carbon-carbon triple bond attached at two positions such as ethynylene (-C:::C-). Examples of alkynyl radicals include ethynyl, propynyl (propargyl), butynyl and the like.

The term lower "alkynyl", alone or in combination, means alkynyl containing from 2 to and including 6 carbon atoms.

The term "alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, ethoxyethoxy, methoxypropoxyethoxy, ethoxypentoxyethoxyethoxy and the like.

The term "cycloalkyl", alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or

tricyclic alkyl radical wherein each cyclic moiety contains preferably from 3 to 10 carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein with respect to the definition of aryl. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like.

The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical as defined above. Examples of such cycloalkylalkyl radicals include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, cyclobutylpropyl, cyclopentylpropyl, cyclohexylbutyl and the like.

The term "benzo", alone or in combination, means the divalent radical  $C_6H_4=$  derived from benzene.

The term "aryl", alone or in combination, or "ara" or "ar" in combination, means a phenyl or naphthyl radical which is optionally substituted with one or more substituents selected from the group consisting of alkyl, alkylcarbonyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl, haloalkylthio, haloalkyloxy, carboxy, alkoxycarbonyl, cycloalkyl, heterocyclo, alkylcarbonylamino, aminoalkanoyl, amido, aminocarbonyl, arylcarbonyl, arylcarbonylamino, aryl, aryloxy, alkyloxycarbonyl, arylalkyloxycarbonyl, alkoxycarbonylamino, substituted amino, disubstituted amino, substituted aminocarbonyl, disubstituted aminocarbonyl, substituted amido, disubstituted amido, aralkoxycarbonylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, alkylsulfinylamino, alkylsulfonylamino, haloalkylsulfinylamino, haloalkylsulfonylamino, arylsulfinylamino,

arylsulfonylamino, heterocyclo, sulfonate, sulfonic acid, trisubstitutedsilyl and the like. It is intended to include both fused ring systems, such as naphthyl and  $\beta$ -carboline, and substituted ring systems, such as biphenyl, phenylpyridyl, naphthyl and diphenylpiperazinyl. Examples of aryl radicals are phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 3-methyl-4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 3-nitrophenyl, 3-aminophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-methyl-3-acetamidophenyl, 4-CF<sub>3</sub>-phenyl, 2-methyl-3-aminophenyl, 4-CF<sub>3</sub>O-phenyl, 3-methyl-4-aminophenyl, 2-amino-3-methylphenyl, 2,4-dimethyl-3-aminophenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, 3-amino-1-naphthyl, 2-methyl-3-amino-1-naphthyl, 6-amino-2-naphthyl, 4,6-dimethoxy-2-naphthyl, piperazinylphenyl and the like.

The terms "aralkyl" and "aralkoxy", alone or in combination, means an alkyl or alkoxy radical as defined above in which at least one hydrogen atom is replaced by an aryl radical as defined above. Thus, "aryl" includes substituents such as benzyl, 2-phenylethyl, dibenzylmethyl, hydroxyphenylmethyl, methylphenylmethyl, and diphenylmethyl, and "aryloxy" includes substituents such as benzyloxy, diphenylmethoxy, 4-methoxyphenylmethoxy and the like.

The term "aralkoxycarbonyl", alone or in combination, means a radical of the formula aralkyl-O-C(O)- in which the term "aralkyl" has the significance given above. Examples of an aralkoxycarbonyl radical are benzyloxycarbonyl and 4-methoxyphenylmethoxycarbonyl.

The term "aryloxy" means a radical of the formula aryl-O- in which the term aryl has the significance given above.

The term "alkanoyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid, examples of which include acetyl, propionyl, butyryl, valeryl, 4-methylvaleryl, and the like.

The term "alkylcarbonyl" means alkanoyl.

The term "cycloalkylcarbonyl" means an acyl radical of the formula cycloalkyl-C(O)- in which the term "cycloalkyl" has the significance give above, such as cyclopropylcarbonyl, cyclohexylcarbonyl, adamantylcarbonyl, 1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl, 1-hydroxy-1,2,3,4-tetrahydro-6-naphthoyl and the like.

The term "aralkanoyl" means an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the like. The term "aroyl" means an acyl radical derived from an arylcarboxylic acid, "aryl" having the meaning given above. Examples of such aroyl radicals include substituted and unsubstituted benzoyl or naphthoyl such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2-naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like.

The term "arylcarbonyl" is aroyl.

Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended.

The term "substituted", when used in combination and not otherwise defined in this paragraph, means one to four substituents attached that are independently selected from the group comprising alkyl, alkylcarbonyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, thiol, haloalkyl, carboxy, alkoxycarbonyl, cycloalkyl, heterocyclo, alkanoylamino, aminoalkanoyl, amido, aminocarbonyl, arylcarbonyl, aryl, aryloxy, alkyloxycarbonyl, arylalkyloxycarbonyl, alkoxycarbonylamino, substituted amino, disubstituted amino,

substituted aminocarbonyl, disubstituted aminocarbonyl,  
substituted amido, disubstituted amido,  
aralkoxycarbonylamino, alkylthio, alkylsulfinyl,  
alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl,  
5 heterocyclo, sulfonate, sulfonic acid and  
trisubstituted silyl. Still other substituents may be  
contemplated by the term "substituted," including the  
various substituents for aryl moieties as described  
hereinabove, some of which may suitably be substituted onto  
10 non-aromatic carbons and other sites on the molecule.

The term "carbonyl", alone includes formyl  $\{-(C=O)-H\}$   
and in combination is a  $-C=O-$  group.

The term "thiocarbonyl", alone includes thioformyl  $\{-(C=S)-H\}$   
and in combination is a  $-C=S-$  group.

15 The term "oxy" means a  $-O-$  group.

The term "carboxy" is  $-COOH$  or the corresponding  
"carboxylate" anion such as is in a carboxylic acid salt.

The term "heterocyclo," alone or in combination, means  
a saturated or partially unsaturated monocyclic, bicyclic or  
20 tricyclic heterocycle radical containing at least one,  
preferably 1 to 4, more preferably 1 to 2, nitrogen, oxygen  
or sulfur atom ring members and having preferably 3 to 8  
ring members in each ring, more preferably 3 to 7 ring  
members in each ring and most preferably 5 to 6 ring members  
25 in each ring. "Heterocyclo" is intended to include  
sulfones, sulfoxides, N-oxides of tertiary nitrogen ring  
members, and carbocyclic fused and benzo fused ring systems.  
Such heterocyclo radicals may be optionally substituted on  
at least one, preferably 1 to 4, more preferably 1 to 2,  
30 carbon atoms by halogen, alkyl, alkoxy, hydroxy, oxo, aryl,  
aralkyl, heteroaryl, heteroaralkyl, amidino, N-alkylamidino,  
alkoxycarbonylamino, alkylsulfonylamino and the like, and/or  
on a secondary nitrogen atom (i.e.,  $-NH-$ ) by hydroxy, alkyl,  
aralkoxycarbonyl, alkanoyl, heteroaralkyl, phenyl or  
35 phenylalkyl, and/or on a tertiary nitrogen atom (i.e.,  $=N-$ )  
by oxido.

The term "heterocycloalkyl" means an alkyl radical as defined above in which at least one hydrogen atom is replaced by a heterocyclo radical as defined above, such as pyrrolidinylmethyl, tetrahydrothienylmethyl, pyridylmethyl and the like.

The term "heteroaryl", alone or in combination, means an aromatic heterocyclo radical as defined above, which is optionally substituted as defined above with respect to the definitions of aryl and heterocyclo. Examples of such heterocyclo and heteroaryl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol 4-yl, 1-benzyloxycarbonylimidazol-4-yl, etc.), pyrazolyl, pyridyl, (e.g., 2-(1-piperidinyl)pyridyl and 2-(4-benzyl piperazin-1-yl-1-pyridinyl, etc.), pyrazinyl, pyrimidinyl, furyl, tetrahydrofuryl, thienyl, tetrahydrothienyl and its sulfoxide and sulfone derivatives, triazolyl, oxazolyl, thiazolyl, indolyl (e.g., 2-indolyl, etc.), quinolinyl, (e.g., 2-quinolinyl, 3-quinolinyl, 1-oxido-2-quinolinyl, etc.), isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, etc.), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydro-2-quinolyl, etc.), 1,2,3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, etc.), quinoxalyl,  $\beta$ -carbolinyl, 2-benzofurancarbonyl, 1-, 2-, 4- or 5-benzimidazolyl, methylenedioxyphen-4-yl, methylenedioxyphen-5-yl, ethylenedioxyphenyl, benzothiazolyl, benzopyranyl, benzofuryl, 2,3-dihydrobenzofuryl, benzoxazolyl, thiophenyl and the like.

The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkoxycarboxylic acid of the formula cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the meaning given above.

The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the meaning given above.



The term "heterocycloalkoxycarbonyl" means an acyl group derived from heterocycloalkyl-O-COOH wherein heterocycloalkyl is as defined above.

5 The term "heterocycloalkanoyl" is an acyl radical derived from a heterocycloalkylcarboxylic acid wherein heterocyclo has the meaning given above.

The term "heterocycloalkanoyl" is an acyl radical derived from a heterocycloalkylcarboxylic acid wherein heterocyclo has the meaning given above.

10 The term "heterocycloalkoxycarbonyl" means an acyl radical derived from a heterocycloalkyl-O-COOH wherein heterocyclo has the meaning given above.

15 The term "heteroaryloxycarbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-O-COOH wherein heteroaryl has the meaning given above.

20 The term "trisubstitutedsilyl", alone or in combination, means a silicone group substituted at its three free valences with groups as listed herein under the definition of substituted amino. Examples include trimethylsilyl, tert-butyldimethylsilyl, triphenylsilyl and the like. The terms "sulfonate", "sulfonic acid" and "sulfonic", alone or in combination, mean the -SO<sub>3</sub>H group and its anion as the sulfonic acid is used in salt formation.

25 The term "aminocarbonyl" alone or in combination, means an amino-substituted carbonyl (carbamoyl) group wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like.

30 The term "amido", alone or in combination, means the product of the combination of a carboxylic acid with an amine as defined herein.

35 The term "amino", alone or in combination, means an -N= group wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals

and the like. Primary amino has two free valences as hydrogen, i.e.,  $\text{-NH}_2$ . Secondary amino, which is also mono-substituted amino or N-substituted amino, has one free valence substituted as above. Tertiary amino, which is also disubstituted amino or N,N-disubstituted amino, has two free valences substituted as above. For example,  $\text{-NH}_2$  is unsubstituted amino,  $\text{-N(H)(CH}_3\text{)}$  is mono-substituted amino (N-methylamino) and  $\text{-N(CH}_3\text{)(CH}_2\text{phenyl)}$  is disubstituted amino (N-methyl-N-benzylamino).

10 The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkylcarboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like.

15 The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "haloalkyl", alone or in combination, means an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen.

20 Haloalkylene means a halohydrocarbonyl group attached at two or more positions. Examples include fluoromethylene ( $\text{-CFH-}$ ), difluoromethylene ( $\text{-CF}_2\text{-}$ ), chloromethylene ( $\text{-CHCl-}$ ) and the like. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl, perfluorodecyl and the like.

25 The term "lowerhaloalkyl", alone or in combination, means haloalkyl containing from 1 to and including 6 carbon atoms.

30 The terms "thia" and "thio", alone or in combination, mean a  $\text{-S-}$  group or an ether wherein the oxygen is replaced with a sulfur. The oxidized derivatives of the thio function are included. Examples include alkylthia groups such as methylthia and oxidation products such as the sulfoxide [ $\text{-(S-O)-}$ ] and sulfone [ $\text{-(S-O}_2\text{)-}$ ] derivatives.

35

The term "thiol" means an  $\text{-SH}$  group.

The term "leaving group" (L or W) generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

The definitions above are applied except where exceptions are specified. For example, monohaloalkyl specifically means an alkyl group with one halogen substituent.

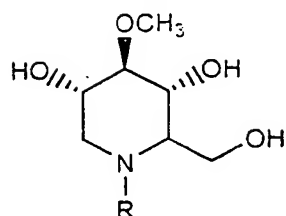
Compounds disclosed herein are those expected to be sufficiently stable to be used as presented herein or to be used in the preparation of the materials shown herein. This specifically includes temporary or transient intermediates in chemical reactions and compounds that may exist in different forms depending upon their environment. It is well known in the art that stability is partially defined in relation to use. For illustration, aldehydes may be hydrated when in an aqueous system but not hydrated in a non-aqueous system and various solvates may be used in pharmaceutical compositions rather than an anhydrous compound. The pharmaceutical chloral is a material wherein the soporific is conveniently administered as the hydrate (chloral hydrate) whereas the anhydrous form (trichloroacetaldehyde) is conveniently used (or made *in situ*) as a reagent or substrate in synthetic reactions such as Wittig reactions.

The present invention comprises any tautomeric forms of compounds of Formula I. The present invention also comprises compounds of Formula I having one or more asymmetric carbons. It is known to those skilled in the art that those imino sugars of the present invention having asymmetric carbon atoms may exist in diastereomeric, racemic, or optically active forms. All of these forms are

contemplated within the scope of this invention. More specifically, the present invention includes enantiomers, diastereomers, racemic mixtures, and other mixtures thereof.

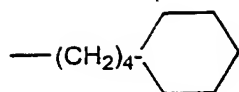
Representative *N*-substituted-imino-D-glucitol compounds  
5 useful in the present invention include, but are not limited to compounds in the Tables:

Table 1

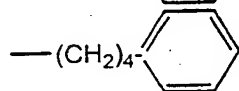


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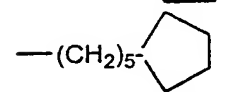
1.



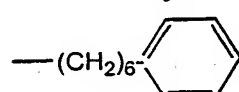
2.



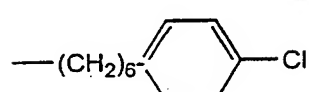
3.



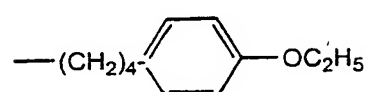
4.



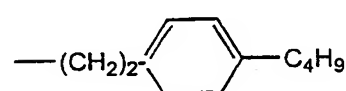
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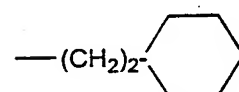
6.



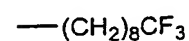
7.



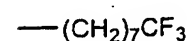
8.



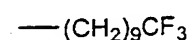
9.



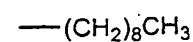
10.



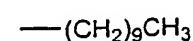
11.



12.

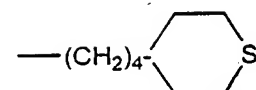


13.

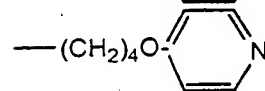


R

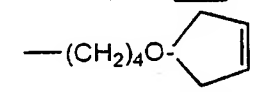
14.



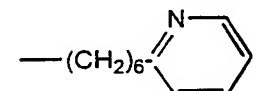
15.



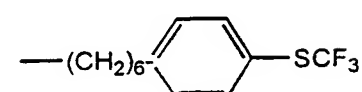
16.



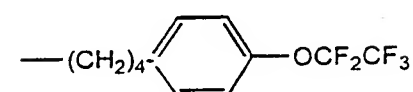
17.



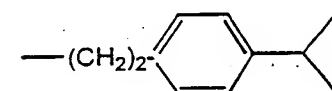
18.



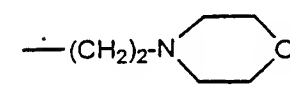
19.



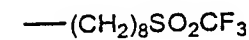
20.



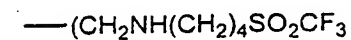
21.



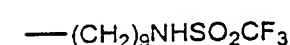
22.



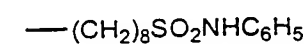
23.



24.



25.



26.

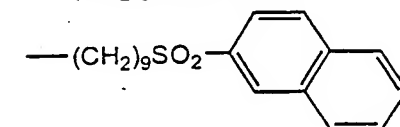
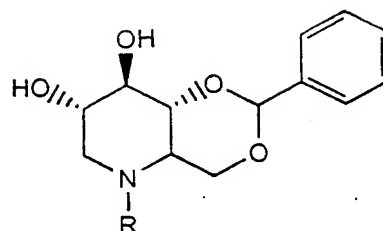


Table 2



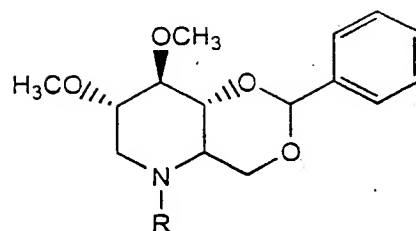
R

1.  $-(CH_2)_4-$
2.  $-(CH_2)_4-$
3.  $-(CH_2)_5-$
4.  $-(CH_2)_6-$
5.  $-(CH_2)_6-$
6.  $-(CH_2)_4-$
7.  $-(CH_2)_2-$
8.  $-(CH_2)_2-$
9.  $-(CH_2)_8CF_3$
10.  $-(CH_2)_7CF_3$
11.  $-(CH_2)_9CF_3$
12.  $-(CH_2)_8CH_3$
13.  $-(CH_2)_9CH_3$

R

14.  $-(CH_2)_4-$
15.  $-(CH_2)_4O-$
16.  $-(CH_2)_4O-$
17.  $-(CH_2)_6-$
18.  $-(CH_2)_6-$
19.  $-(CH_2)_4-$
20.  $-(CH_2)_2-$
21.  $-(CH_2)_2-N$
22.  $-(CH_2)_8SO_2CF_3$
23.  $-(CH_2NH(CH_2)_4SO_2CF_3)$
24.  $-(CH_2)_9NHSO_2CF_3$
25.  $-(CH_2)_8SO_2NHC_6H_5$
26.  $-(CH_2)_9SO_2-$

Table 3



R

R

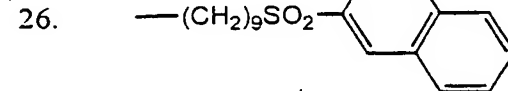
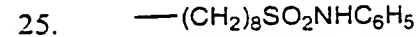
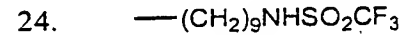
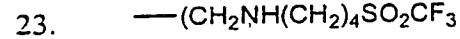
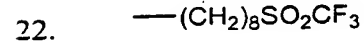
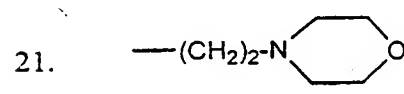
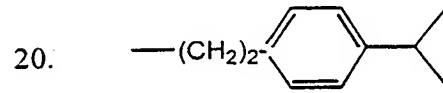
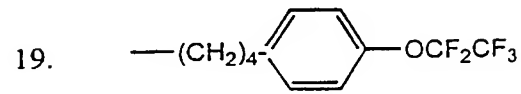
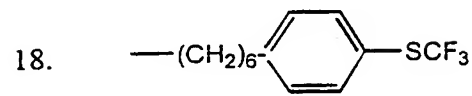
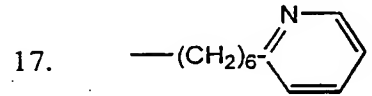
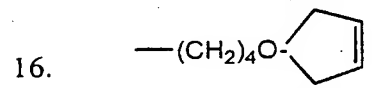
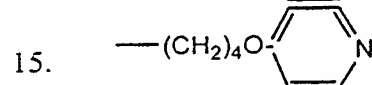
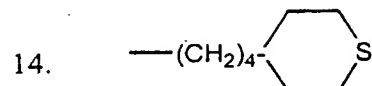
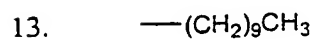
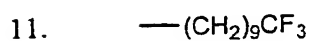
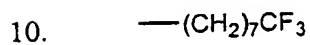
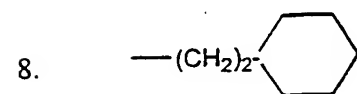
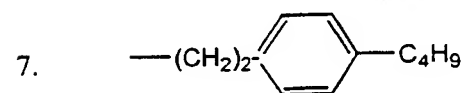
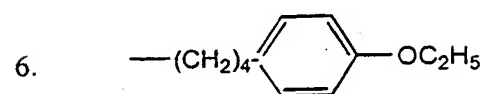
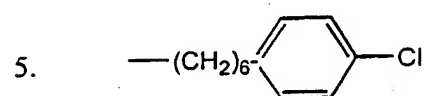
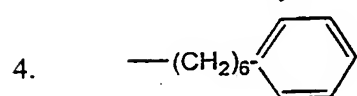
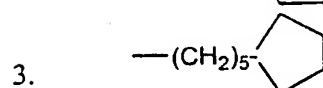
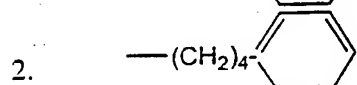
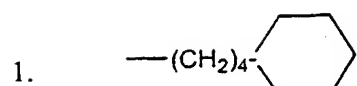
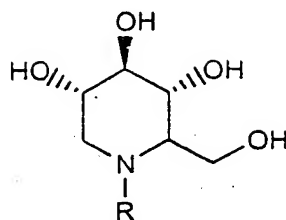


Table 4



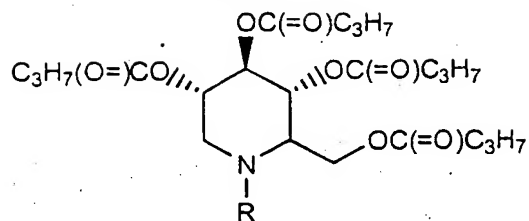
R

R

- |   |  |
|---|--|
| 1. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_6\text{CF}_3$   | 12. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_4\text{NHCH}_2\text{CF}_3$  |
| 2. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{CF}_3$   | 13. $-(\text{CH}_2)_3\text{NH}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$   |
| 3. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OCF}_3$                 | 14. $-(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{OCF}_3$  |
| 4. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OCF}_3$                 | 15. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{OCF}_3$   |
| 5. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CF}_3$                  | 16. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CF}_3$  |
| 6. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$                  | 17. $-(\text{CH}_2)_2\text{N}(\text{CH}_3)(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$                                     |
| 7. $-(\text{CH}_2)_4\text{O}-\text{C}_6\text{H}_4-\text{OCF}_3$                                 | 18. $-(\text{CH}_2)_4\text{S}-\text{C}_6\text{H}_4-\text{OCF}_3$   |
| 8. $-(\text{CH}_2)_6\text{O}-\text{C}_6\text{H}_4-\text{OCF}_3$                                 | 19. $-(\text{CH}_2)_6\text{O}-\text{C}_6\text{H}_4-\text{SCF}_3$   |
| 9. $-(\text{CH}_2)_6\text{S}(\text{CH}_2)_2\text{CF}_3$   | 20. $-(\text{CH}_2)_6\text{N}(\text{CH}_2\text{C}_6\text{H}_5)(\text{CH}_2)_2\text{CF}_3$  |
| 10. $-(\text{CH}_2)_4\text{S}(\text{CH}_2)_2\text{CF}_3$  | 22. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3(\text{OCF}_3)_2$                  |
| 11. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_5$ | 22. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{C}(=\text{O})-\text{OCH}_3$ |



Table 5

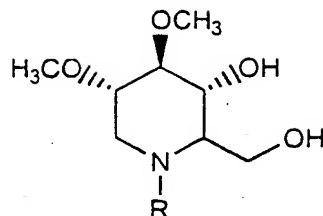


R

R

- |   |   |
|---|---|
| 1. $-(CH_2)_2O(CH_2)_6CF_3$                           | 12. $-(CH_2)_2S(CH_2)_4NHCH_2CF_3$                                |
| 2. $-(CH_2)_6O(CH_2)_2CF_3$                           | 13. $-(CH_2)_3NH(CH_2)_2O(CH_2)_2CF_3$                            |
| 3. $-(CH_2)_2O(CH_2)_2O(CH_2)_2OCF_3$                 | 14. $-(CH_2)_2NH(CH_2)_2S(CH_2)_2OCF_3$                           |
| 4. $-(CH_2)_6O(CH_2)_2O(CH_2)_2OCF_3$                 | 15. $-(CH_2)_6O(CH_2)_2S(CH_2)_2OCF_3$                            |
| 5. $-(CH_2)_2O(CH_2)_2O(CH_2)_3CF_3$                  | 16. $-(CH_2)_2S(CH_2)_2O(CH_2)_3CF_3$                             |
| 6. $-(CH_2)_2O(CH_2)_2O(CH_2)_2CF_3$                  | 17. $-(CH_2)_2N(CH_3)(CH_2)_2O(CH_2)_2CF_3$                       |
| 7. $-(CH_2)_4O-\text{C}_6\text{H}_4-OCF_3$            | 18. $-(CH_2)_4S-\text{C}_6\text{H}_4-OCF_3$                       |
| 8. $-(CH_2)_6O-\text{C}_6\text{H}_4-OCF_3$            | 19. $-(CH_2)_6O-\text{C}_6\text{H}_4-SCF_3$                       |
| 9. $-(CH_2)_6S(CH_2)_2CF_3$                           | 20. $-(CH_2)_6N(CH_2C_6H_5)(CH_2)_2CF_3$                          |
| 10. $-(CH_2)_4S(CH_2)_2CF_3$                          | 22. $-(CH_2)_2O(CH_2)_2NH-C(=O)-\text{C}_6\text{H}_3(OCF_3)_2$    |
| 11. $-(CH_2)_2O(CH_2)_2NH-C(=O)-\text{C}_6\text{H}_5$ | 22. $-(CH_2)_2O(CH_2)_2NH-C(=O)-\text{C}_6\text{H}_4-C(=O)-OCH_3$ |

Table 6

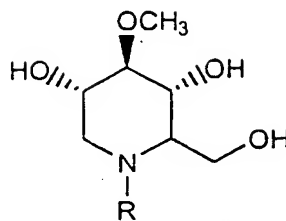


R

R

- |   |  |
|---|--|
| 1. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_6\text{CF}_3$   | 12. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_4\text{NHCH}_2\text{CF}_3$  |
| 2. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{CF}_3$   | 13. $-(\text{CH}_2)_3\text{NH}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$   |
| 3. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OCF}_3$                 | 14. $-(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{OCF}_3$  |
| 4. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OCF}_3$                 | 15. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{OCF}_3$   |
| 5. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CF}_3$                  | 16. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CF}_3$  |
| 6. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$                  | 17. $-(\text{CH}_2)_2\text{N}(\text{CH}_3)(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$   |
| 7. $-(\text{CH}_2)_4\text{O}-\text{C}_6\text{H}_4-\text{OCF}_3$                                 | 18. $-(\text{CH}_2)_4\text{S}-\text{C}_6\text{H}_4-\text{OCF}_3$   |
| 8. $-(\text{CH}_2)_6\text{O}-\text{C}_6\text{H}_4-\text{OCF}_3$                                 | 19. $-(\text{CH}_2)_6\text{O}-\text{C}_6\text{H}_4-\text{SCF}_3$   |
| 9. $-(\text{CH}_2)_6\text{S}(\text{CH}_2)_2\text{CF}_3$   | 20. $-(\text{CH}_2)_6\text{N}(\text{CH}_2\text{C}_6\text{H}_5)(\text{CH}_2)_2\text{CF}_3$  |
| 10. $-(\text{CH}_2)_4\text{S}(\text{CH}_2)_2\text{CF}_3$  | 22. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{OCF}_3$                                 |
| 11. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_5$ | 22. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{C}(=\text{O})-\text{C}(\text{OCH}_3)_2$ |

Table 7

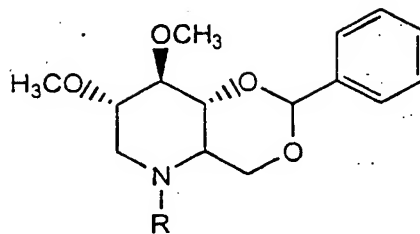


R

R

- |   |  |
|---|--|
| 1. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_6\text{CF}_3$   | 12. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_4\text{NHCH}_2\text{CF}_3$  |
| 2. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{CF}_3$   | 13. $-(\text{CH}_2)_3\text{NH}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$   |
| 3. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OCF}_3$                 | 14. $-(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{OCF}_3$  |
| 4. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OCF}_3$                 | 15. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{OCF}_3$   |
| 5. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CF}_3$                  | 16. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CF}_3$  |
| 6. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$                  | 17. $-(\text{CH}_2)_2\text{N}(\text{CH}_3)(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$                                     |
| 7. $-(\text{CH}_2)_4\text{O}-\text{C}_6\text{H}_4-\text{OCF}_3$                                 | 18. $-(\text{CH}_2)_4\text{S}-\text{C}_6\text{H}_4-\text{OCF}_3$   |
| 8. $-(\text{CH}_2)_6\text{O}-\text{C}_6\text{H}_4-\text{OCF}_3$                                 | 19. $-(\text{CH}_2)_6\text{O}-\text{C}_6\text{H}_4-\text{SCF}_3$   |
| 9. $-(\text{CH}_2)_6\text{S}(\text{CH}_2)_2\text{CF}_3$   | 20. $-(\text{CH}_2)_6\text{N}(\text{CH}_2\text{C}_6\text{H}_5)(\text{CH}_2)_2\text{CF}_3$  |
| 10. $-(\text{CH}_2)_4\text{S}(\text{CH}_2)_2\text{CF}_3$  | 22. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{OCF}_3$                     |
| 11. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_5$ | 22. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{C}(=\text{O})-\text{OCH}_3$ |

Table 8

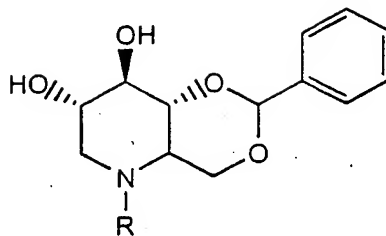


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- |   |   |
|---|---|
| 1. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_6\text{CF}_3$   | 12. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_4\text{NHCH}_2\text{CF}_3$   |
| 2. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{CF}_3$   | 13. $-(\text{CH}_2)_3\text{NH}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$                                |
| 3. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OCF}_3$                 | 14. $-(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{OCF}_3$                               |
| 4. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OCF}_3$                 | 15. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{OCF}_3$                                |
| 5. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CF}_3$                  | 16. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CF}_3$                                 |
| 6. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$                  | 17. $-(\text{CH}_2)_2\text{N}(\text{CH}_3)(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$                    |
| 7. $-(\text{CH}_2)_4\text{O}-\text{C}_6\text{H}_4-\text{OCF}_3$                                 | 18. $-(\text{CH}_2)_4\text{S}-\text{C}_6\text{H}_4-\text{OCF}_3$  |
| 8. $-(\text{CH}_2)_6\text{O}-\text{C}_6\text{H}_4-\text{OCF}_3$                                 | 19. $-(\text{CH}_2)_6\text{O}-\text{C}_6\text{H}_4-\text{SCF}_3$  |
| 9. $-(\text{CH}_2)_6\text{S}(\text{CH}_2)_2\text{CF}_3$   | 20. $-(\text{CH}_2)_6\text{N}(\text{CH}_2\text{C}_6\text{H}_5)(\text{CH}_2)_2\text{CF}_3$                       |
| 10. $-(\text{CH}_2)_4\text{S}(\text{CH}_2)_2\text{CF}_3$  | 22. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_3(\text{OCF}_3)_2$ |
| 11. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_5$ | 22. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}(\text{OCH}_3)=\text{CH}_2$   |

Table 9

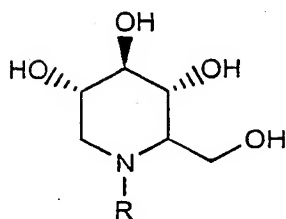


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- |   |  |
|---|--|
| 1. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_6\text{CF}_3$   | 12. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_4\text{NHCH}_2\text{CF}_3$  |
| 2. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{CF}_3$   | 13. $-(\text{CH}_2)_3\text{NH}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$   |
| 3. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OCF}_3$                 | 14. $-(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{OCF}_3$  |
| 4. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OCF}_3$                 | 15. $-(\text{CH}_2)_6\text{O}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{OCF}_3$   |
| 5. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CF}_3$                  | 16. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CF}_3$  |
| 6. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$                  | 17. $-(\text{CH}_2)_2\text{N}(\text{CH}_3)(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CF}_3$                                     |
| 7. $-(\text{CH}_2)_4\text{O}-\text{C}_6\text{H}_4-\text{OCF}_3$                                 | 18. $-(\text{CH}_2)_4\text{S}-\text{C}_6\text{H}_4-\text{OCF}_3$   |
| 8. $-(\text{CH}_2)_6\text{O}-\text{C}_6\text{H}_4-\text{OCF}_3$                                 | 19. $-(\text{CH}_2)_6\text{O}-\text{C}_6\text{H}_4-\text{SCF}_3$   |
| 9. $-(\text{CH}_2)_6\text{S}(\text{CH}_2)_2\text{CF}_3$   | 20. $-(\text{CH}_2)_6\text{N}(\text{CH}_2\text{C}_6\text{H}_5)(\text{CH}_2)_2\text{CF}_3$  |
| 10. $-(\text{CH}_2)_4\text{S}(\text{CH}_2)_2\text{CF}_3$  | 22. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{OCF}_3$                     |
| 11. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_5$ | 22. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{C}(=\text{O})-\text{OCH}_3$ |

Table 10



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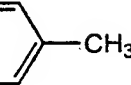
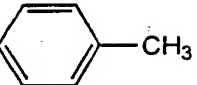
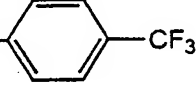
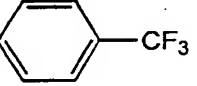

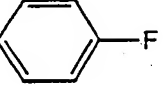


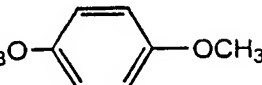
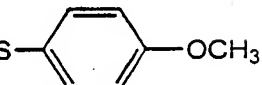
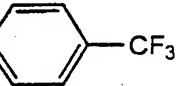
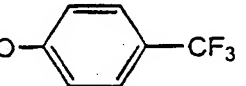



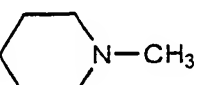
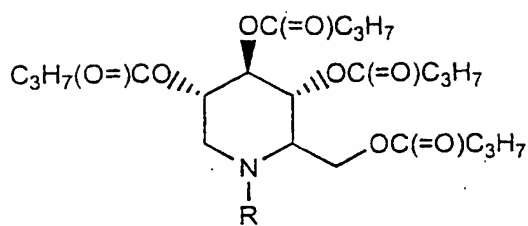
- |   |  |
|---|--|
| 1. $-(CH_2)_{11}CF_3$   | 12. $-(CH_2)_8(CF_2)_3CF_3$  |
| 2. $-(CH_2)_7O(CH_2)_2OCH_2CF_3$  | 13. $-(CH_2)_7O(CH_2)_2OCF_2CF_3$  |
| 3. $-(CH_2)_4O(CH_2)_4CF_3$   | 14. $-(CH_2)_4O(CH_2)_2(CF_2)_2CF_3$   |
| 4. $-(CH_2)_4OCH_2-$         | 15. $-(CH_2)_4OCF_2-$         |
| 5. $-(CH_2)_4OCH_2-$       | 16. $-(CH_2)_4SCF_2-$       |
| 6. $-(CH_2)_4OCH_2-$       | 17. $-(CH_2)_4OCH_2-$       |
| 7. $-(CH_2)_5O(CH_2)_3-$   | 18. $-(CH_2)_5O(CF_2)_3-$   |
| 8. $-(CH_2)_2O(CH_2)_3O-$  | 19. $-(CH_2)_2S(CH_2)_3S-$  |
| 9. $-(CH_2)_2O(CH_2)_2O-$  | 20. $-(CH_2)_2S(CH_2)_2O-$  |
| 10. $-(CH_2)_2O(CH_2)_2-$  | 21. $-(CH_2)_2S(CH_2)_2-$   |
| 11. $-(CH_2)_4O-$          | 22. $-(CH_2)_4O-$           |

Table 11



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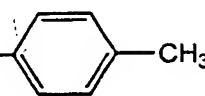
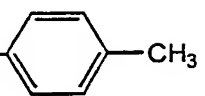
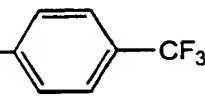
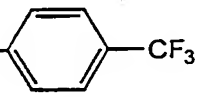
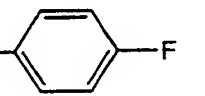
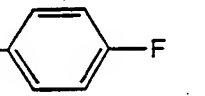


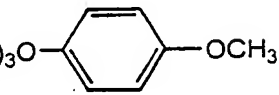
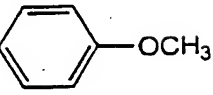
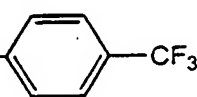
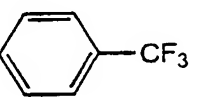
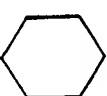


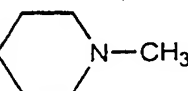
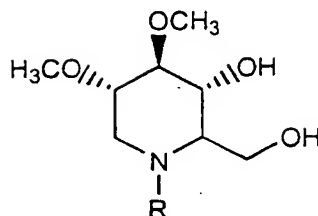
- |   |  |
|---|--|
| 1. $-(CH_2)_{11}CF_3$   | 12. $-(CH_2)_8(CF_2)_3CF_3$  |
| 2. $-(CH_2)_7O(CH_2)_2OCH_2CF_3$  | 13. $-(CH_2)_7O(CH_2)_2OCF_2CF_3$  |
| 3. $-(CH_2)_4O(CH_2)_4CF_3$   | 14. $-(CH_2)_4O(CH_2)_2(CF_2)_2CF_3$   |
| 4. $-(CH_2)_4OCH_2-$        | 15. $-(CH_2)_4OCF_2-$        |
| 5. $-(CH_2)_4OCH_2-$       | 16. $-(CH_2)_4SCF_2-$       |
| 6. $-(CH_2)_4OCH_2-$       | 17. $-(CH_2)_4OCH_2-$       |
| 7. $-(CH_2)_5O(CH_2)_3-$   | 18. $-(CH_2)_5O(CF_2)_3-$   |
| 8. $-(CH_2)_2O(CH_2)_3O-$  | 19. $-(CH_2)_2S(CH_2)_3S-$  |
| 9. $-(CH_2)_2O(CH_2)_2O-$  | 20. $-(CH_2)_2S(CH_2)_2O-$  |
| 10. $-(CH_2)_2O(CH_2)_2-$  | 21. $-(CH_2)_2S(CH_2)_2-N$  |
| 11. $-(CH_2)_4O-$          | 22. $-(CH_2)_4O-$           |

Table 12



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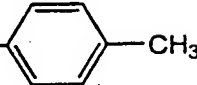
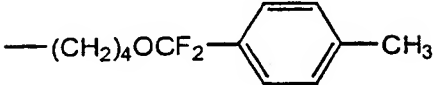
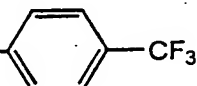
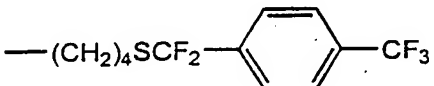
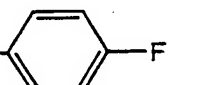
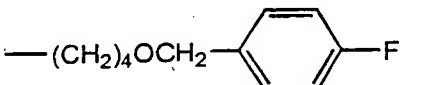

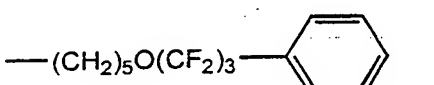
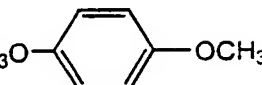
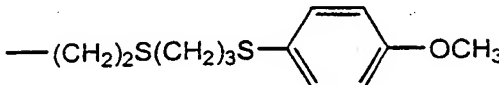
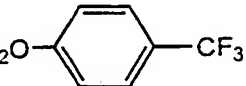
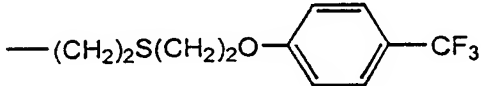

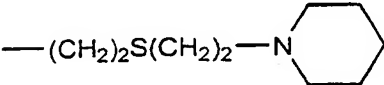
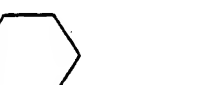
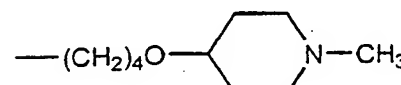
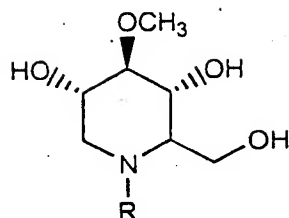
- |  |   |
|--|---|
| 1. $-(\text{CH}_2)_{11}\text{CF}_3$  | 12. $-(\text{CH}_2)_8(\text{CF}_2)_3\text{CF}_3$  |
| 2. $-(\text{CH}_2)_7\text{O}(\text{CH}_2)_2\text{OCH}_2\text{CF}_3$  | 13. $-(\text{CH}_2)_7\text{O}(\text{CH}_2)_2\text{OCF}_2\text{CF}_3$  |
| 3. $-(\text{CH}_2)_4\text{O}(\text{CH}_2)_4\text{CF}_3$  | 14. $-(\text{CH}_2)_4\text{O}(\text{CH}_2)_2(\text{CF}_2)_2\text{CF}_3$   |
| 4. $-(\text{CH}_2)_4\text{OCH}_2$ -                       | 15. $-(\text{CH}_2)_4\text{OCF}_2$ -                       |
| 5. $-(\text{CH}_2)_4\text{OCH}_2$ -                     | 16. $-(\text{CH}_2)_4\text{SCF}_2$ -                     |
| 6. $-(\text{CH}_2)_4\text{OCH}_2$ -                     | 17. $-(\text{CH}_2)_4\text{OCH}_2$ -                     |
| 7. $-(\text{CH}_2)_5\text{O}(\text{CH}_2)_3$ -          | 18. $-(\text{CH}_2)_5\text{O}(\text{CF}_2)_3$ -          |
| 8. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{O}$ -  | 19. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_3\text{S}$ -  |
| 9. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}$ -  | 20. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{O}$ -  |
| 10. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ -         | 21. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2$ -          |
| 11. $-(\text{CH}_2)_4\text{O}$ -                        | 22. $-(\text{CH}_2)_4\text{O}$ -                         |



Table 13



R

R

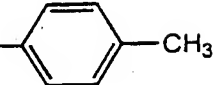
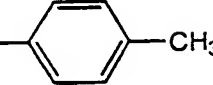
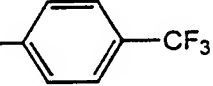
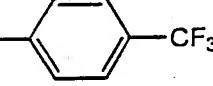
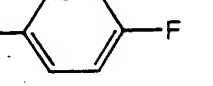
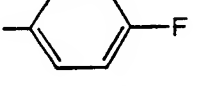
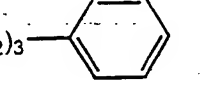
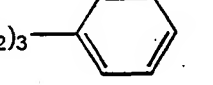
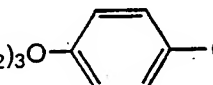
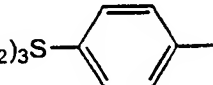
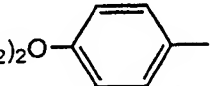
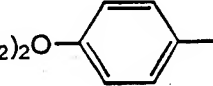

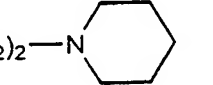
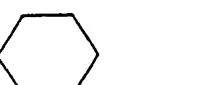
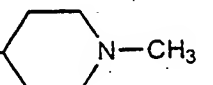
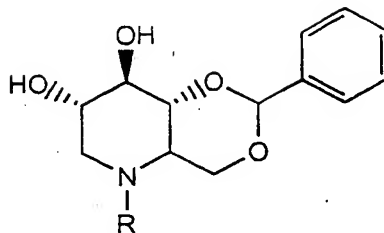
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|--|---|
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| 2. $-(\text{CH}_2)_7\text{O}(\text{CH}_2)_2\text{OCH}_2\text{CF}_3$  | 13. $-(\text{CH}_2)_7\text{O}(\text{CH}_2)_2\text{OCF}_2\text{CF}_3$  |
| 3. $-(\text{CH}_2)_4\text{O}(\text{CH}_2)_4\text{CF}_3$  | 14. $-(\text{CH}_2)_4\text{O}(\text{CH}_2)_2(\text{CF}_2)_2\text{CF}_3$   |
| 4. $-(\text{CH}_2)_4\text{OCH}_2$ -                       | 15. $-(\text{CH}_2)_4\text{OCF}_2$ -                       |
| 5. $-(\text{CH}_2)_4\text{OCH}_2$ -                     | 16. $-(\text{CH}_2)_4\text{SCF}_2$ -                     |
| 6. $-(\text{CH}_2)_4\text{OCH}_2$ -                     | 17. $-(\text{CH}_2)_4\text{OCH}_2$ -                     |
| 7. $-(\text{CH}_2)_5\text{O}(\text{CH}_2)_3$ -          | 18. $-(\text{CH}_2)_5\text{O}(\text{CF}_2)_3$ -          |
| 8. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{O}$ -  | 19. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_3\text{S}$ -  |
| 9. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}$ -  | 20. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{O}$ -  |
| 10. $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ -         | 21. $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2$ -          |
| 11. $-(\text{CH}_2)_4\text{O}$ -                        | 22. $-(\text{CH}_2)_4\text{O}$ -                         |

Table 14



R

R

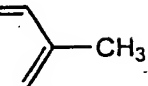
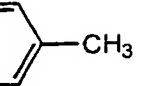
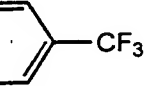
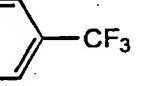
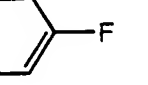
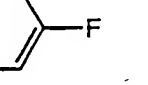
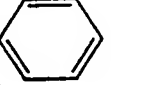
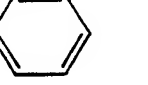
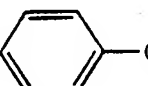
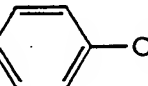
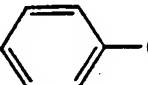
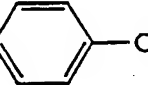

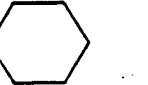

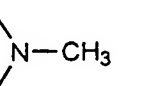
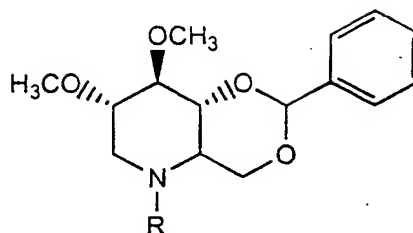
- |  |   |
|--|---|
| 1. $-(CH_2)_{11}CF_3$  | 12. $-(CH_2)_8(CF_2)_3CF_3$   |
| 2. $-(CH_2)_7O(CH_2)_2OCH_2CF_3$   | 13. $-(CH_2)_7O(CH_2)_2OCF_2CF_3$   |
| 3. $-(CH_2)_4O(CH_2)_4CF_3$  | 14. $-(CH_2)_4O(CH_2)_2(CF_2)_2CF_3$  |
| 4. $-(CH_2)_4OCH_2-$  $-CH_3$         | 15. $-(CH_2)_4OCF_2-$  $-CH_3$         |
| 5. $-(CH_2)_4OCH_2-$  $-CF_3$        | 16. $-(CH_2)_4SCF_2-$  $-CF_3$        |
| 6. $-(CH_2)_4OCH_2-$  $-F$          | 17. $-(CH_2)_4OCH_2-$  $-F$          |
| 7. $-(CH_2)_5O(CH_2)_3-$            | 18. $-(CH_2)_5O(CF_2)_3-$            |
| 8. $-(CH_2)_2O(CH_2)_3O-$  $-OCH_3$ | 19. $-(CH_2)_2S(CH_2)_3S-$  $-OCH_3$ |
| 9. $-(CH_2)_2O(CH_2)_2O-$  $-CF_3$  | 20. $-(CH_2)_2S(CH_2)_2O-$  $-CF_3$  |
| 10. $-(CH_2)_2O(CH_2)_2-$           | 21. $-(CH_2)_2S(CH_2)_2-$            |
| 11. $-(CH_2)_4O-$                   | 22. $-(CH_2)_4O-$  $-N-CH_3$         |

Table 15



R

R

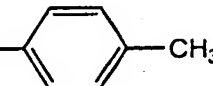
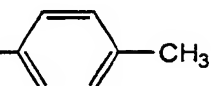
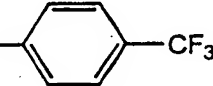
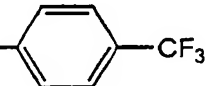
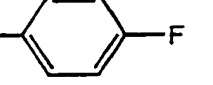
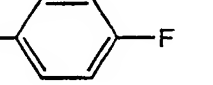
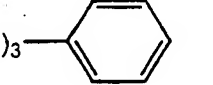

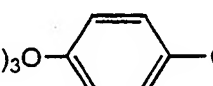

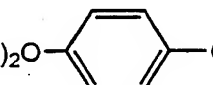



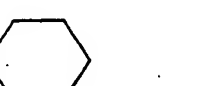
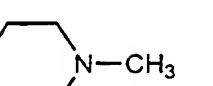
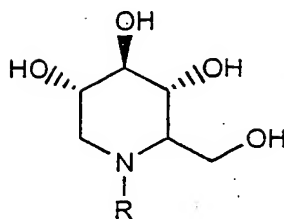
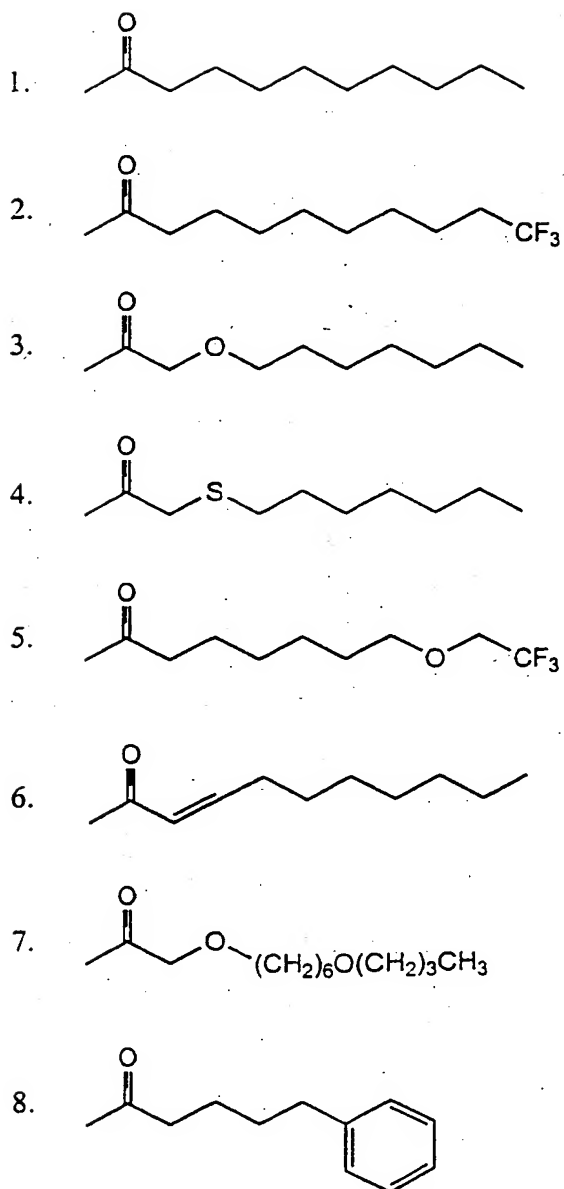
- |  |   |
|--|---|
| 1. $-(CH_2)_{11}CF_3$  | 12. $-(CH_2)_8(CF_2)_3CF_3$   |
| 2. $-(CH_2)_7O(CH_2)_2OCH_2CF_3$   | 13. $-(CH_2)_7O(CH_2)_2OCF_2CF_3$   |
| 3. $-(CH_2)_4O(CH_2)_4CF_3$  | 14. $-(CH_2)_4O(CH_2)_2(CF_2)_2CF_3$  |
| 4. $-(CH_2)_4OCH_2$ -         | 15. $-(CH_2)_4OCF_2$ -         |
| 5. $-(CH_2)_4OCH_2$ -        | 16. $-(CH_2)_4SCF_2$ -        |
| 6. $-(CH_2)_4OCH_2$ -       | 17. $-(CH_2)_4OCH_2$ -       |
| 7. $-(CH_2)_5O(CH_2)_3$ -   | 18. $-(CH_2)_5O(CF_2)_3$ -   |
| 8. $-(CH_2)_2O(CH_2)_3O$ -  | 19. $-(CH_2)_2S(CH_2)_3S$ -  |
| 9. $-(CH_2)_2O(CH_2)_2O$ -  | 20. $-(CH_2)_2S(CH_2)_2O$ -  |
| 10. $-(CH_2)_2O(CH_2)_2$ -  | 21. $-(CH_2)_2S(CH_2)_2$ -   |
| 11. $-(CH_2)_4O$ -          | 22. $-(CH_2)_4O$ -           |

Table 16



R



R

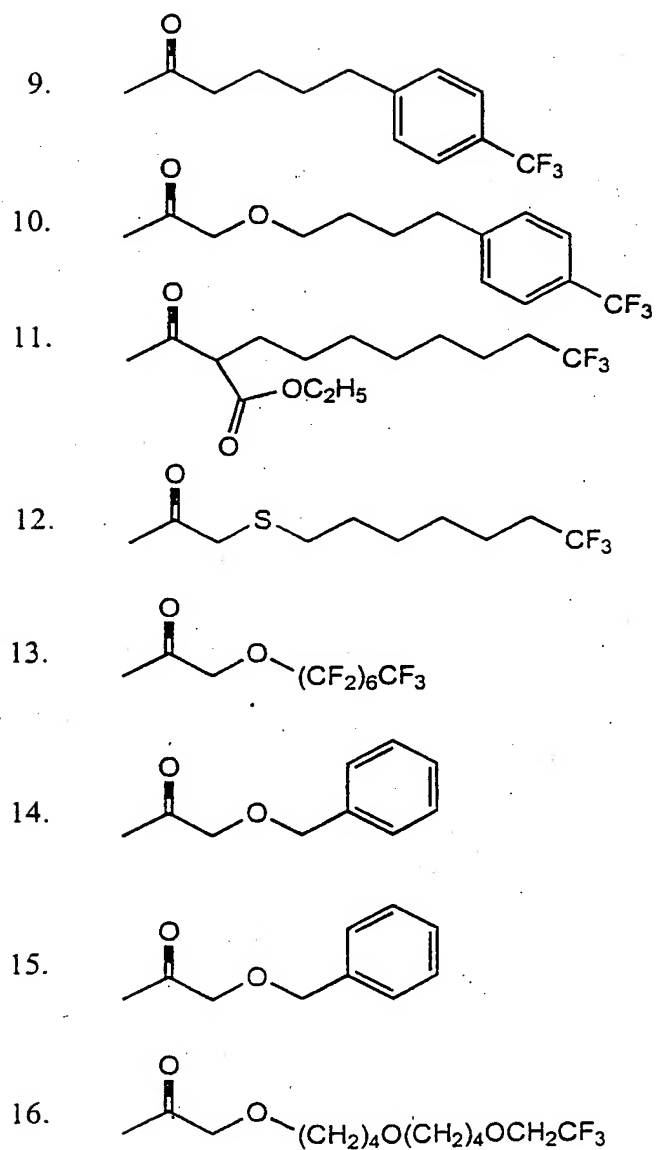
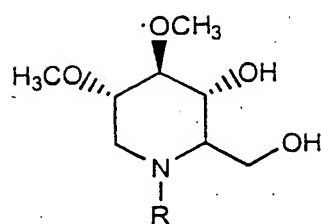
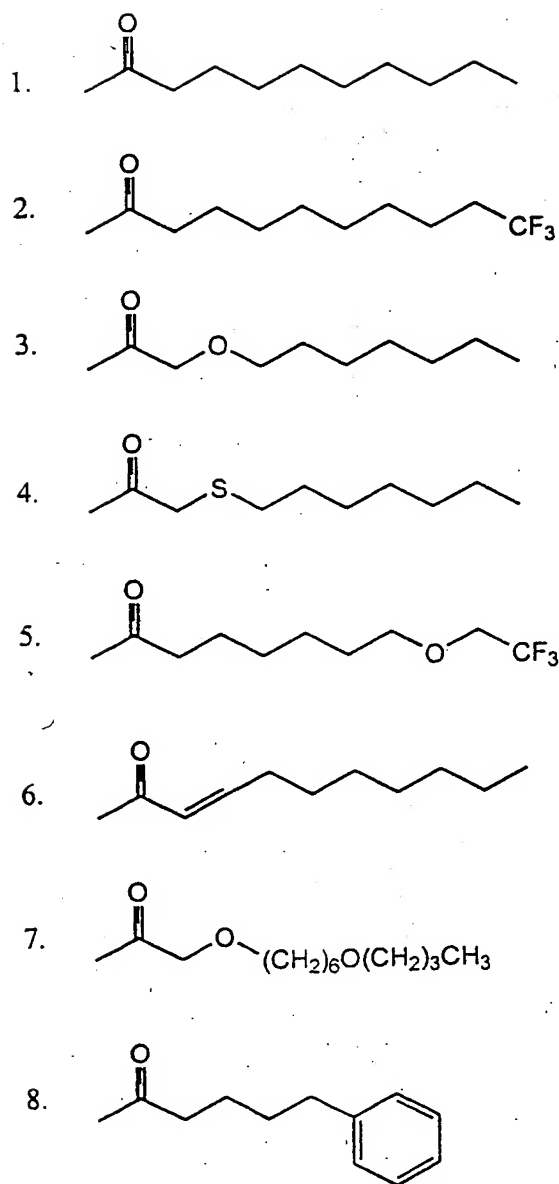


Table 17



R



R

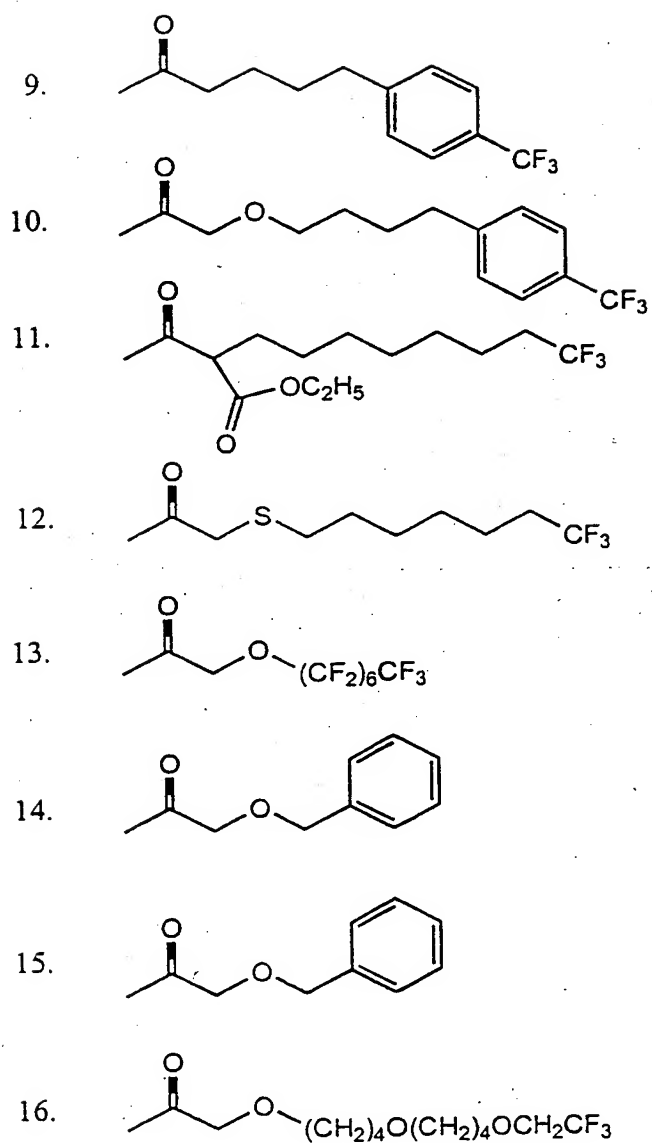
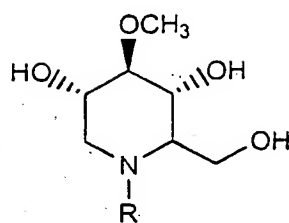
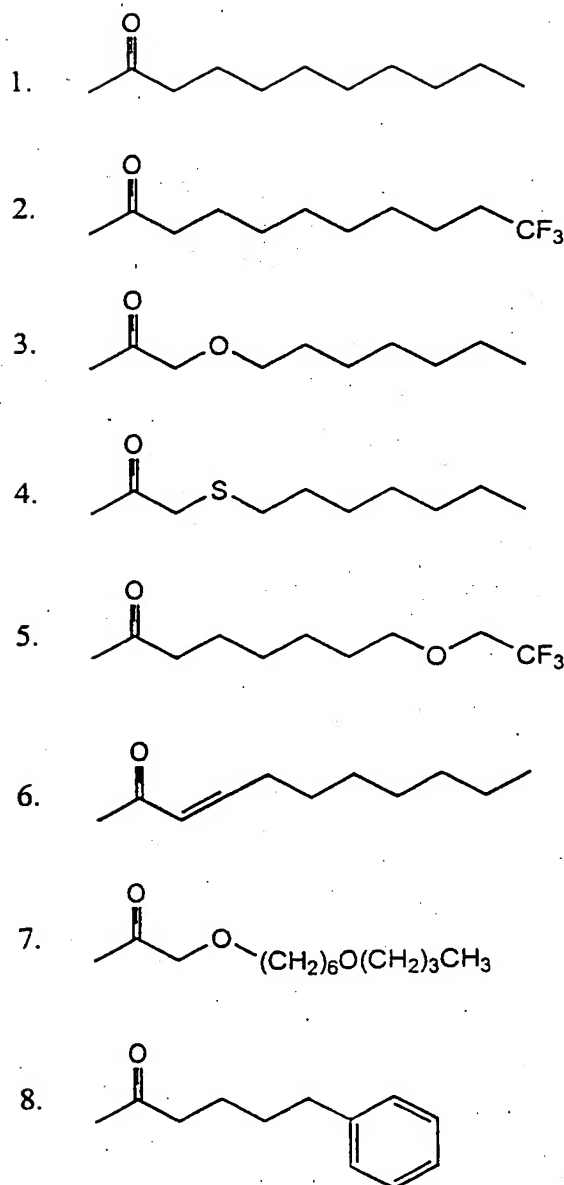


Table 18



R



R

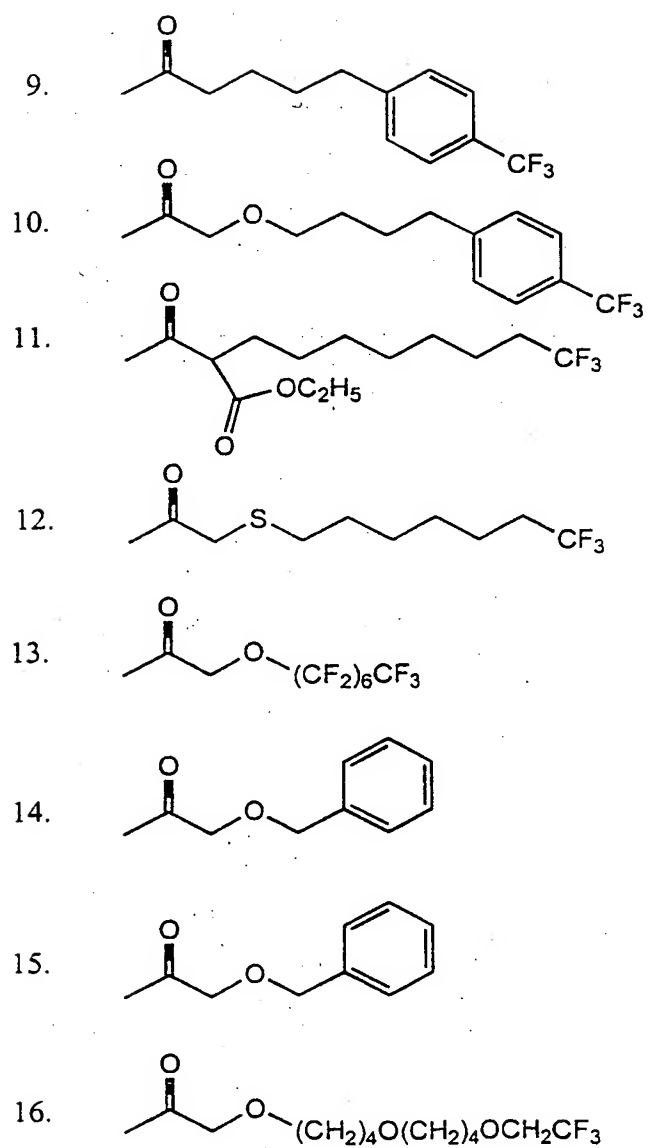
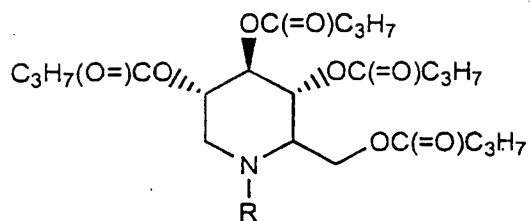
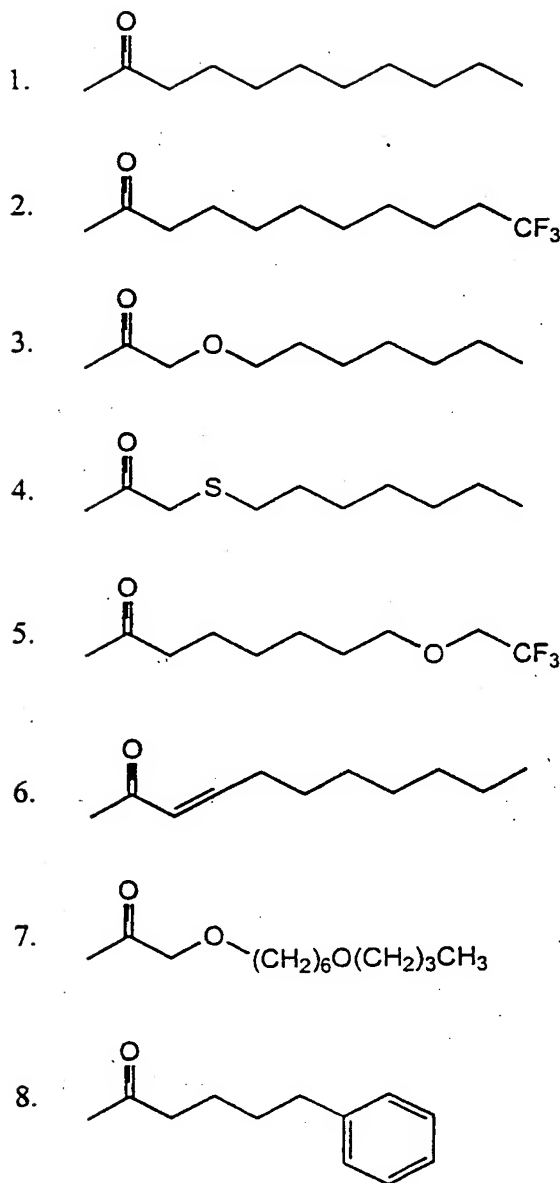


Table 19



R



R

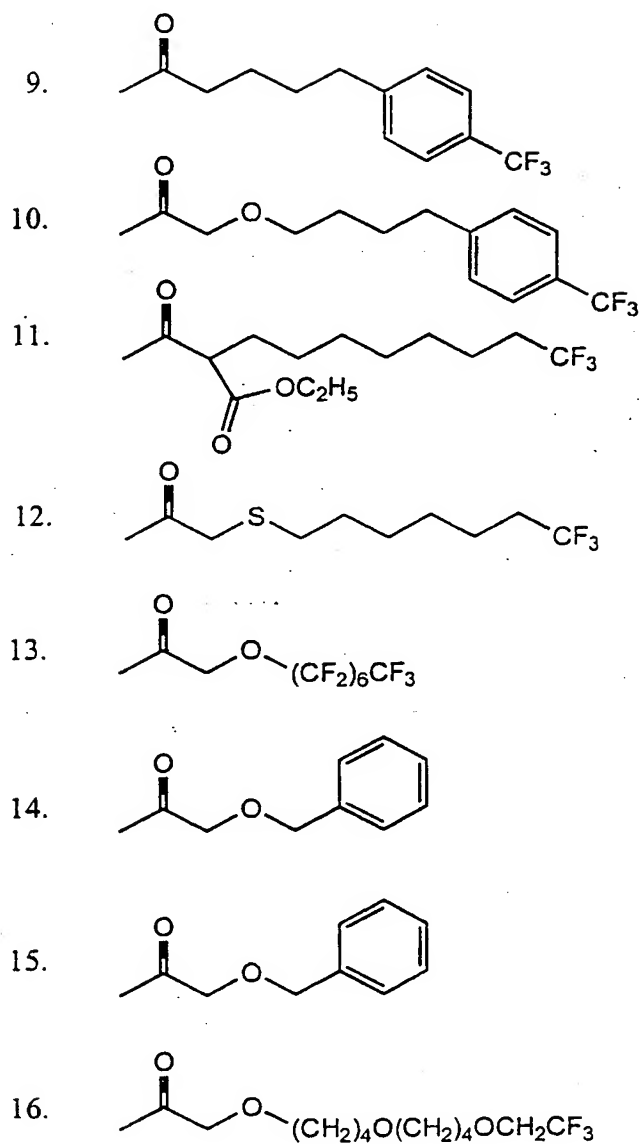
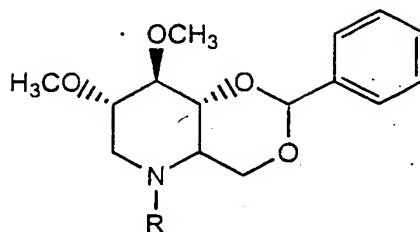
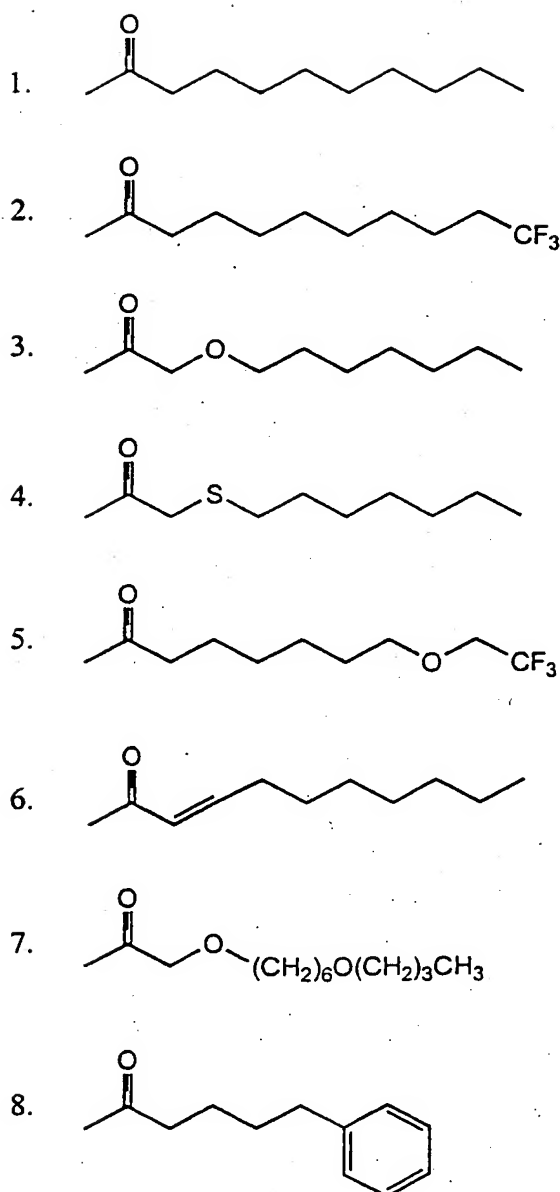


Table 20



R



R

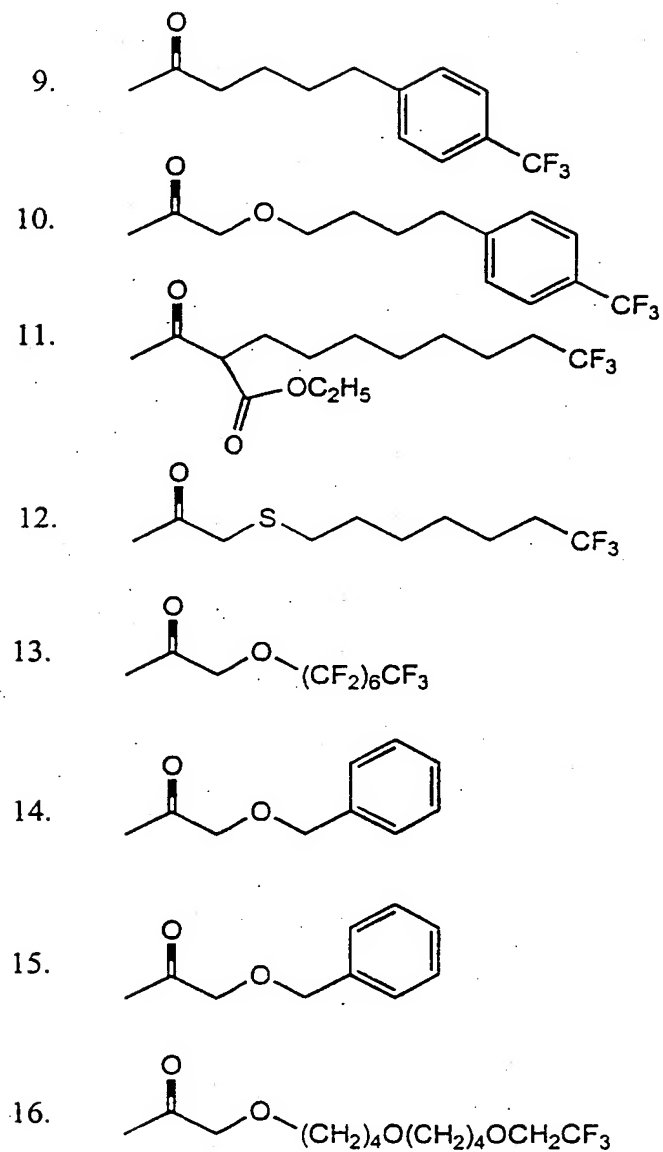
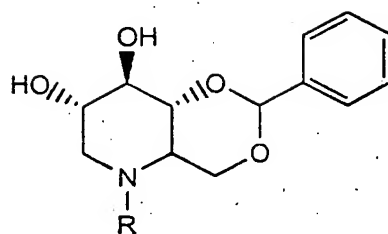
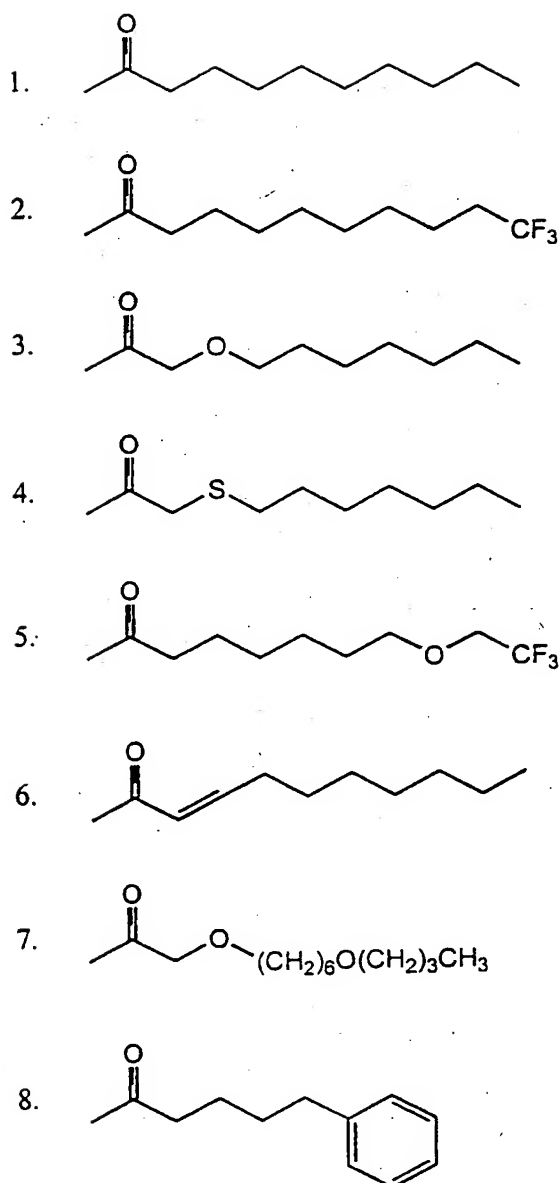




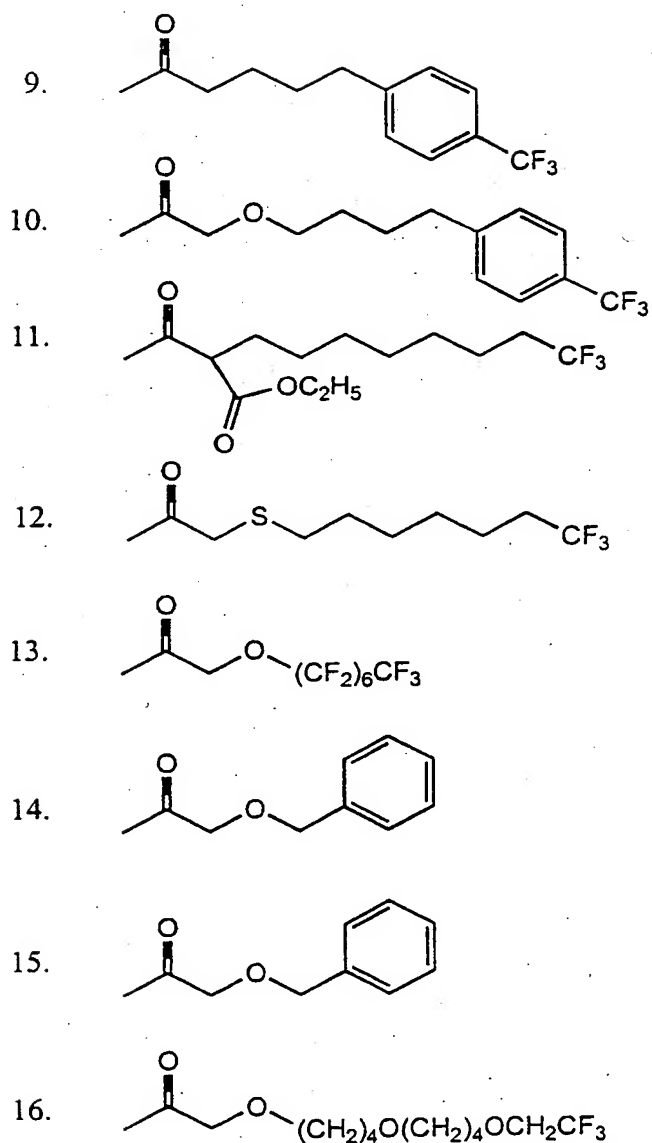
Table 21



R



R



Among the substituents that may constitute R in the compounds of Formula I, certain classes are preferred. For example, to provide a compound which in its free base form is relatively strongly alkaline, it is advantageous for R to be selected from among:

Table 22

	aryloxyalkoxyalkyl	aminothiocarbonylalkyl
	alkylcarbonyloxyalkyl	aminosulfonealkyl
	substituted alkyl	arylalkynyl
10	arylcarbonyloxyalkyl	heterocycloalkyl
	alkylcarbonylaminoalkyl	heteroarylalkyl
		heteroaryloxyalkyl
	arylcarbonylaminoalkyl	heteroarylthiaalkyl
	alkoxycarbonylamino-	heterocyclooxyalkyl
15	alkyl	heterocyclothiaalkyl
	aminothiocarbonyl-	aryloxyalkyl
		arylthiaalkyl
	aminothiocarbonyl-	monohaloalkyl
	aminoalkyl	haloalkyloxyalkyl
20	alkenyl	cycloalkyloxyalkyl
	arylalkenyl	cycloalkylalkyloxyalkyl
	carboxyalkyl	
	alkoxycarbonylalkyl	perhaloalkylaralkyl
	aminocarbonylalkyl	

Salts of such compounds with strong pharmaceutically acceptable acids provide highly dissociable compounds that are effective in the method of the invention. More preferably, R may be selected from among: aryl, arylcarbonylaminoalkyl, aminocarbonylaminoalkyl, alkenyl, arylalkenyl, arylalkynyl, heterocycloalkyl, heteroarylalkyl, heteroaryloxyalkyl, heterocyclooxyalkyl, aryloxyalkyl, arylthiaalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl and perhaloalkylaralkyl; of which alkyl, alkenyl, arylalkenyl, heterocycloalkyl,

heteroarylalkyl, heteroaryloxyalkyl, heterocyclooxyalkyl, aryloxyalkyl, haloalkyloxyalkyl and perhaloalkylaralkyl are particularly preferred, and alkenyl, arylalkenyl, heterocycloalkyl, heteroarylalkyl, aryloxyalkyl  
 5 haloalkyloxyalkyl, perhaloalkylaralkyl and cycloalkyloxyalkyl are most preferred.

However, amidoglucitol compounds of Formula I and pharmaceutically acceptable salts thereof are also useful in the treatment of hepatitis infections, or alternatively in  
 10 the synthesis of other compounds of Formula I that are effective for such treatment. Thus, members of the following group of amido and other substituents may also serve effectively as the N-substituent (R) in the compounds of Formula I:

15

Table 23

carbonyl	alkylcarbonyloxyalkyl-
alkenylcarbonyl	carbonyl
alkynylcarbonyl	arylcarbonyloxyalkyl-
arylalkylcarbonyl	carbonyl
20 aryloxyalkylcarbonyl	aminoalkylcarbonyl
haloalkylcarbonyl	alkylcarbonylamino-
hydroxyalkylcarbonyl	alkylcarbonyl
haloalkyloxyalkyl-	arylcarbonylaminoalkyl-
carbonyl	carbonyl
25 cycloalkyloxyalkyl-	
carbonyl	alkoxycarbonylamino-
alkoxyalkylcarbonyl	alkylcarbonyl
cycloalkylalkylcarbonyl	aminocarbonylaminoalkyl-
alkoxycarbonyl	carbonyl
30 substituted alkyl-	aminothiocarbonylamino-
carbonyl	alkylcarbonyl
aryloxyalkoxyalkyl-	arylalkenylcarbonyl
carbonyl	carboxyalkylcarbonyl
	alkoxycarbonylalkyl-

	carbonyl	carbonyl
	aminocarbonylalkyl-	
	carbonyl	
	aminothiocabonyl-	
5	alkylcarbonyl	
	aminosulfonealkyl-	
	carbonyl	
	arylalkynylcarbonyl	
	heterocycloalkylcarbonyl	
10	heteroarylalkylcarbonyl	
	heteroaryloxyalkylcarbonyl	
	heteroarylthiaalkyl-	
	carbonyl	
	heterocyclooxyalkyl-	
15	carbonyl	
	heterocyclothiaalkyl-	
	carbonyl	
	arylthiaalkylcarbonyl	
	monohaloalkylcarbonyl	
20	haloalkyloxyalkyl-	
	carbonyl	
	cycloalkylalkyloxyalkyl-	

More preferably, R may be selected from among:

25	alkenylcarbonyl, arylalkylcarbonyl, haloalkylcarbonyl,
	haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl,
	alkoxyalkylcarbonyl, cycloalkylalkylcarbonyl, alkyl-
	carbonyl, aminoalkylcarbonyl, arylalkenylcarbonyl,
	aminosulfonealkylcarbonyl, arylalkynylcarbonyl,
30	heterocycloalkylcarbonyl, heteroarylalkylcarbonyl,
	heteroaryloxyalkylcarbonyl, heterocyclooxyalkylcarbonyl,
	arylthiaalkylcarbonyl, haloalkyloxyalkylcarbonyl,
	cycloalkylalkyloxyalkyl; of which alkenylcarbonyl,
	arylalkylcarbonyl, haloalkylcarbonyl,

haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, cycloalkylalkylcarbonyl, alkyl-carbonyl, aminoalkylcarbonyl, arylalkenylcarbonyl, heterocycloalkylcarbonyl, heteroarylalkylcarbonyl, heteroaryloxyalkylcarbonyl and haloalkyloxyalkylcarbonyl are particularly preferred, and arylalkylcarbonyl, haloalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkylalkylcarbonyl, aminoalkylcarbonyl and haloalkyloxycarbonyl are most preferred either as antiviral compounds or as intermediates from which such compounds are prepared.

N-substituents which may be preferred for purposes of potency, efficacy, formulation ability, toxicity and/or cost include:

15

Table 24

aryloxyalkoxyalkyl	heterocycloalkyl
substituted alkyl	heteroarylalkyl
aminoalkyl	heteroaryloxyalkyl
arylcarbonylaminoalkyl	heteroarylthiaalkyl
20 alkoxycarbonylamino-alkyl	heterocyclooxyalkyl
aminocarbonylamino-alkyl	heterocyclothiaalkyl
alkenyl	aryloxyalkyl
25 arylalkenyl	arylthiaalkyl
aminocarbonylalkyl	monohaloalkyl
aminosulfonealkyl	haloalkyloxyalkyl
arylalkynyl	cycloalkyloxyalkyl
	cycloalkylalkyloxyalkyl

Certain compounds of Formula I are novel compounds of this invention. Novel compounds of Formula I include compounds in which R is among the following:

Table 25

	aryloxyalkyl	arylalkyloxycarbonyl
	substituted-	aryloxyalkylcarbonyl
	aryloxyalkyl	substituted aryloxy-
5	monohaloalkyl	alkylcarbonyl
	haloalkyloxyalkyl	haloalkylcarbonyl
	carbonyl	hydroxyalkylcarbonyl
	cycloalkyloxyalkyl	haloalkyloxyalkyl-
	cycloalkylalkyloxyalkyl	carbonyl
10	alkenylcarbonyl	cycloalkyloxyalkyl-
	alkynylcarbonyl	carbonyl
	arylalkylcarbonyl	alkoxyalkylcarbonyl
	substituted-	
	arylalkylcarbonyl	

15 Of the compounds of Table 25, the substituted alkyls are basic compounds which are advantageous in forming stable, water soluble, non-volatile pharmaceutically acceptable salts, preferably with strong acids. The carbonyl compounds of Table 25, like those of Table 23, are adapted for use

20 either as antiviral therapeutic compounds or as intermediates for the preparation of other N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds of the invention and/or useful in the methods thereof. Of the carbonyl compounds of Table 25, arylalkylcarbonyl,

25 aryloxyalkylcarbonyl, haloalkylcarbonyl, haloalkyloxyalkylcarbonyl, and cycloalkyloxyalkylcarbonyl are the more preferred.

Another identifiable class of particularly preferred compounds are those in which R is R<sup>5</sup>, and especially

30 compounds wherein R is selected from among aryloxyalkyl, monoalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, and cycloalkylalkyloxyalkyl.

In another useful group of compounds, R is selected from among alkenylcarbonyl, alkynylcarbonyl,

arylalkylcarbonyl, arylalkyloxycarbonyl,  
aryloxyalkylcarbonyl, haloalkylcarbonyl,  
hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl,  
cycloalkyloxyalkylcarbonyl, and alkoxyalkylcarbonyl.

5 Compounds in which R is R<sup>5</sup> are highly preferred,  
especially the ethers (where each of any of X<sup>1</sup> through X<sup>4</sup>  
are oxygen or sulfur, preferably oxygen), R<sup>1</sup> is alkyl or  
haloalkyl, and each of any of R<sup>2</sup> through R<sup>4</sup> and R<sup>6</sup> is  
10 independently alkylene or haloalkylene. The di- and  
triethers are particularly preferred, as are the R<sup>5</sup>  
substituents in which R<sup>1</sup> is trifluoroalkyl.

Compounds in which A, B, C, and D are hydrido are  
particularly preferred for administration in the treatment  
of hepatitis infections. However, compounds with other  
15 combinations of A, B, C and D substituents and  
configurations (including ring structures as described  
hereinabove) are useful as therapeutic agents and as  
intermediates for the synthesis of other compounds of  
Formula I. Where used as therapeutic agents, many of these  
20 substituted imino sugars, especially the esters and ethers,  
function as prodrugs.

Particular advantageous combinations of A, B, C, and D  
include those in which, for example: (i) A, B and C are  
hydrido and D and R taken together may form a five membered  
25 ring when R is carbonyl or a six membered ring when R is  
alkylcarbonyl; (ii) A and B taken together with the atoms to  
which they are attached form a five or six membered  
heterocyclic ring and C and D are hydrido; (iii) A and B are  
hydrido, lower alkyl, lower haloalkyl or acyl, and C and D  
30 taken together with the atoms to which they are attached  
form a five or six membered heterocyclic ring.

Advantageous properties as intermediates, direct action  
pharmaceuticals, and/or prodrugs are provided by compounds  
which combine a substituent from each of the preferred  
35 groups which may constitute R, as defined in R<sup>5</sup> and/or  
Tables 1 through 4, with each of the configurations of A, B,

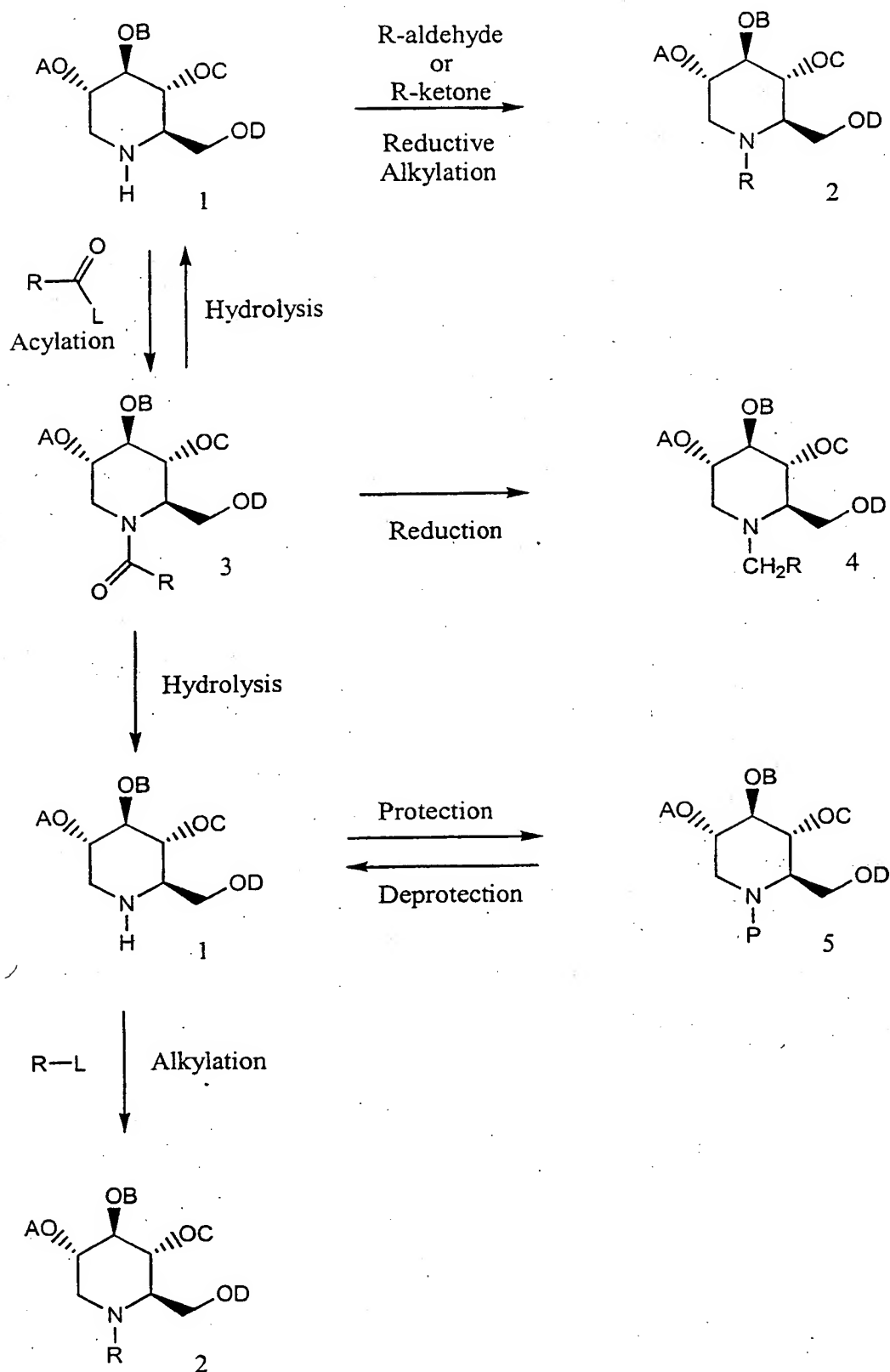
C and D as outlined in enumerated combinations (i) through (iii) above.

The substituted-imino-D-glucitol compounds, including pro-drugs, useful in the present invention, can be prepared by methods well known in the art. U.S. Patent 4,260,622  
5 discloses the preparation of numerous compounds and U. S. Patent 5,401,645 shows the preparation of glucamine precursors of iminosugars and their conversion into substituted iminosugars. Additional documents relevant to  
10 the preparation of substituted-imino-D-glucitol compounds and pro-drugs include U.S. Patents Nos. 4,182,767, 4,260,622, 4,611,058, 4,639,436, and 5,003,072, 5,411,970, 5,806,650 and 5,151,519; PCT International Publication WO 95/19172; and Tan et al. (1991) Journal of Biological  
15 Chemistry 266(22):14504-14510; and the references cited therein. Methods for introducing oxygen into alkyl side chains are disclosed in Tan et al., (1994) Glycobiology 4(2):141-149, and van den Broek et al. (1994) Recl. Trav. Chim. Pays-Bas 113:107-116 discloses the preparation of  
20 ether oxygen-containing DNJ compounds. Starting material such as DNJ (deoxynojirimycin) are also commercially available (Sigma Chemical Co (1989) catalog number D-1282.

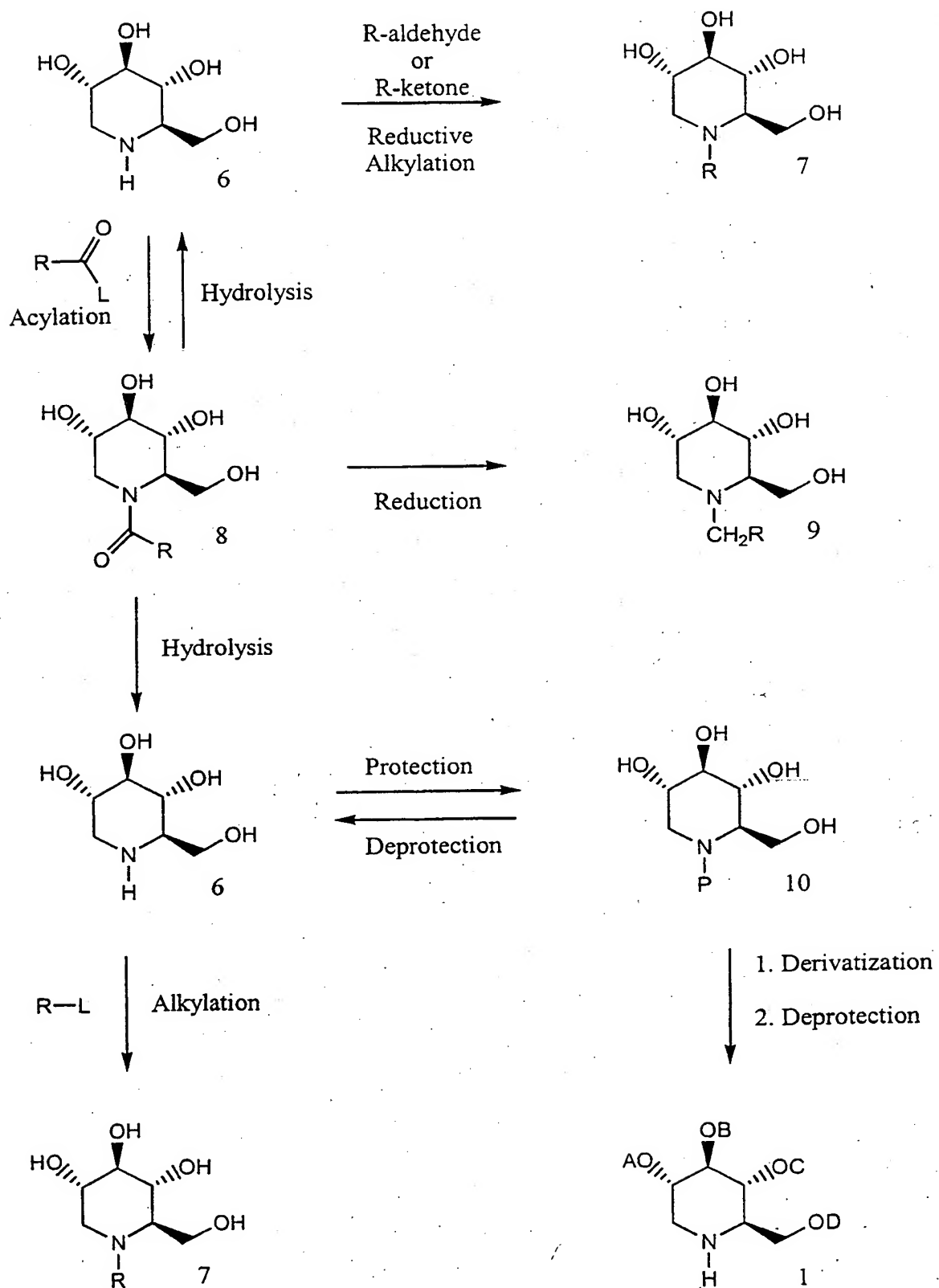
Non-limiting illustrative preparation procedures are presented below in Examples 1 and 2 and Scheme 1 through and  
25 including Scheme 5.



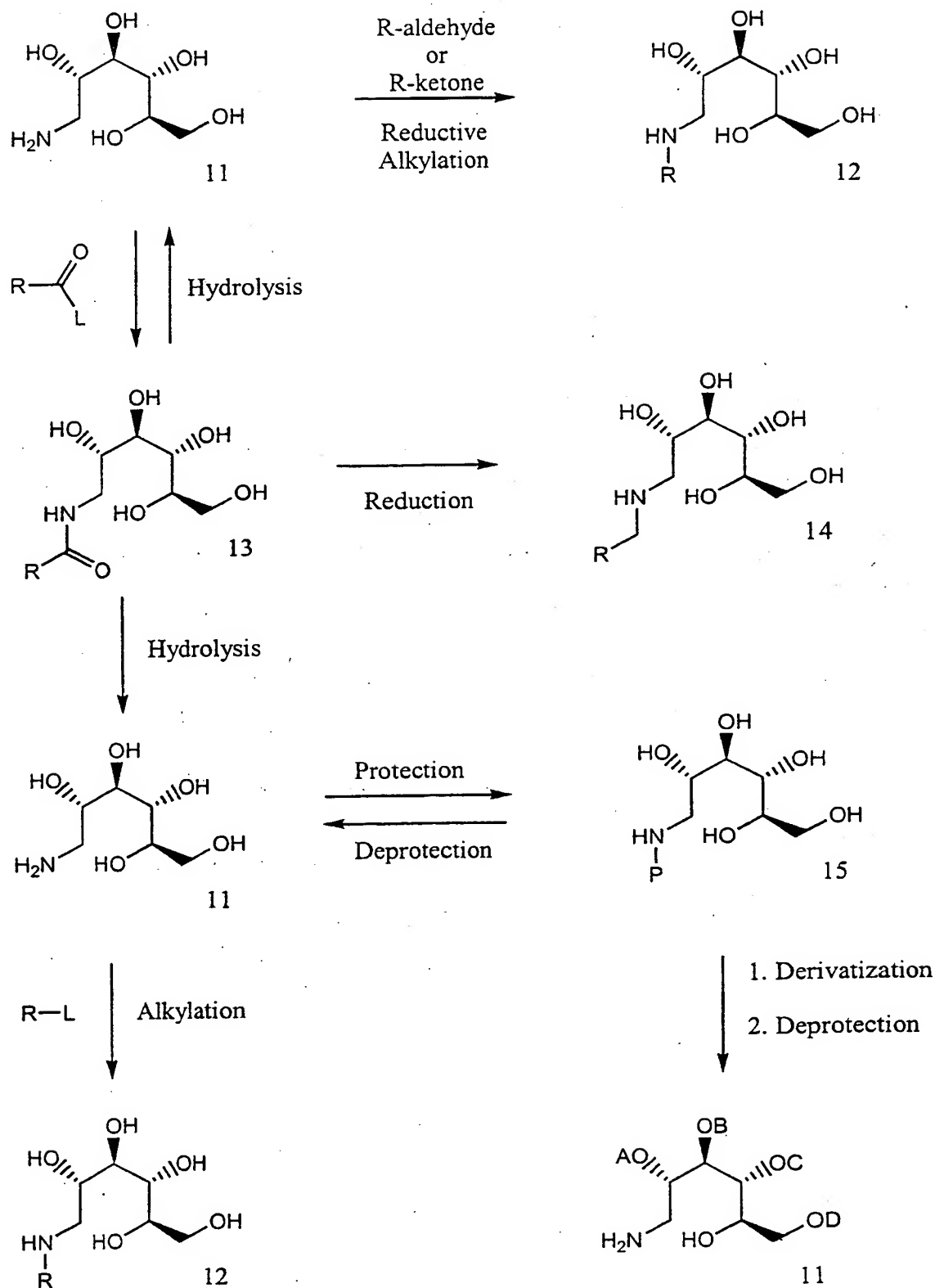
## SCHEME 1



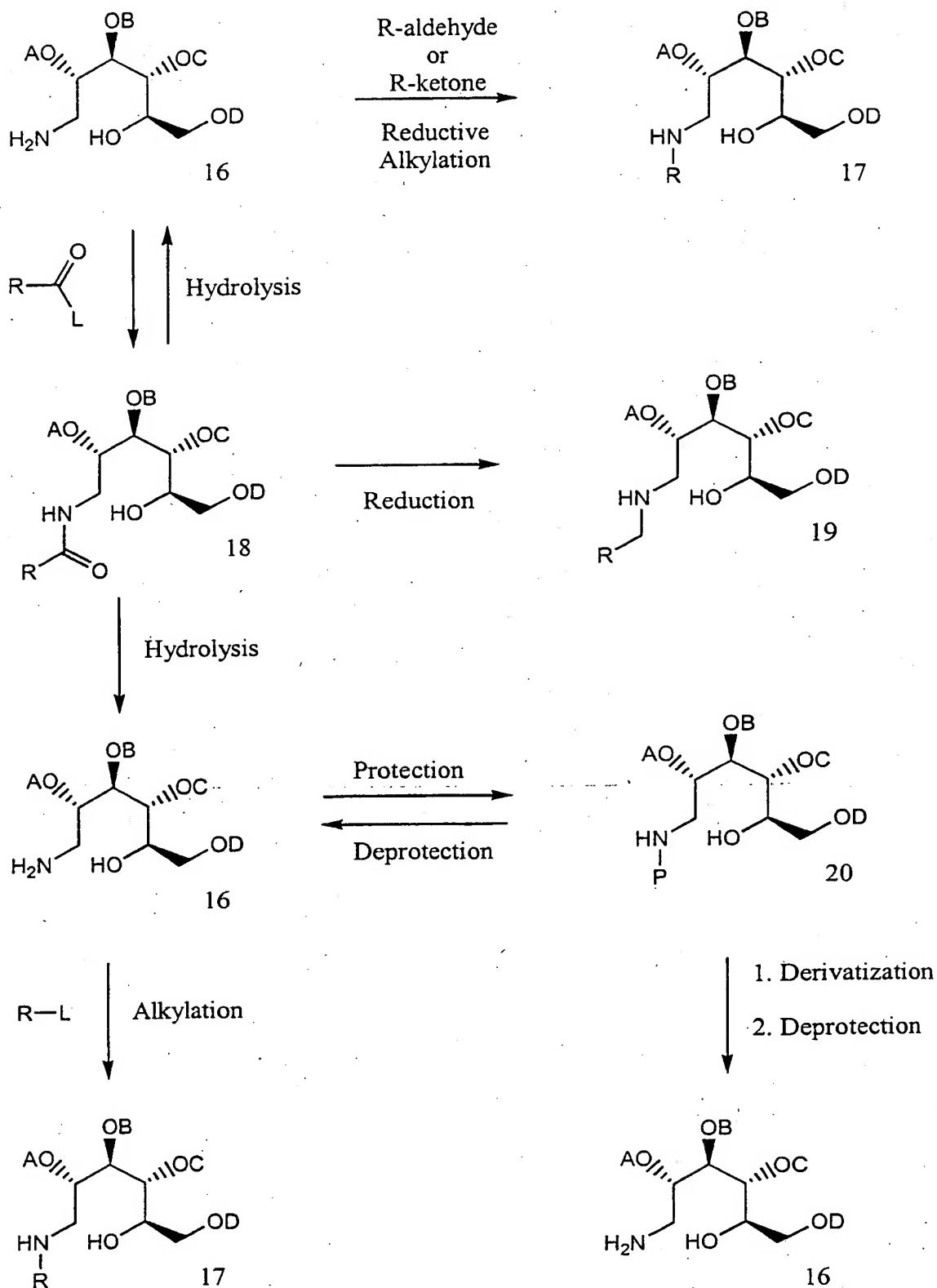
## SCHEME 2



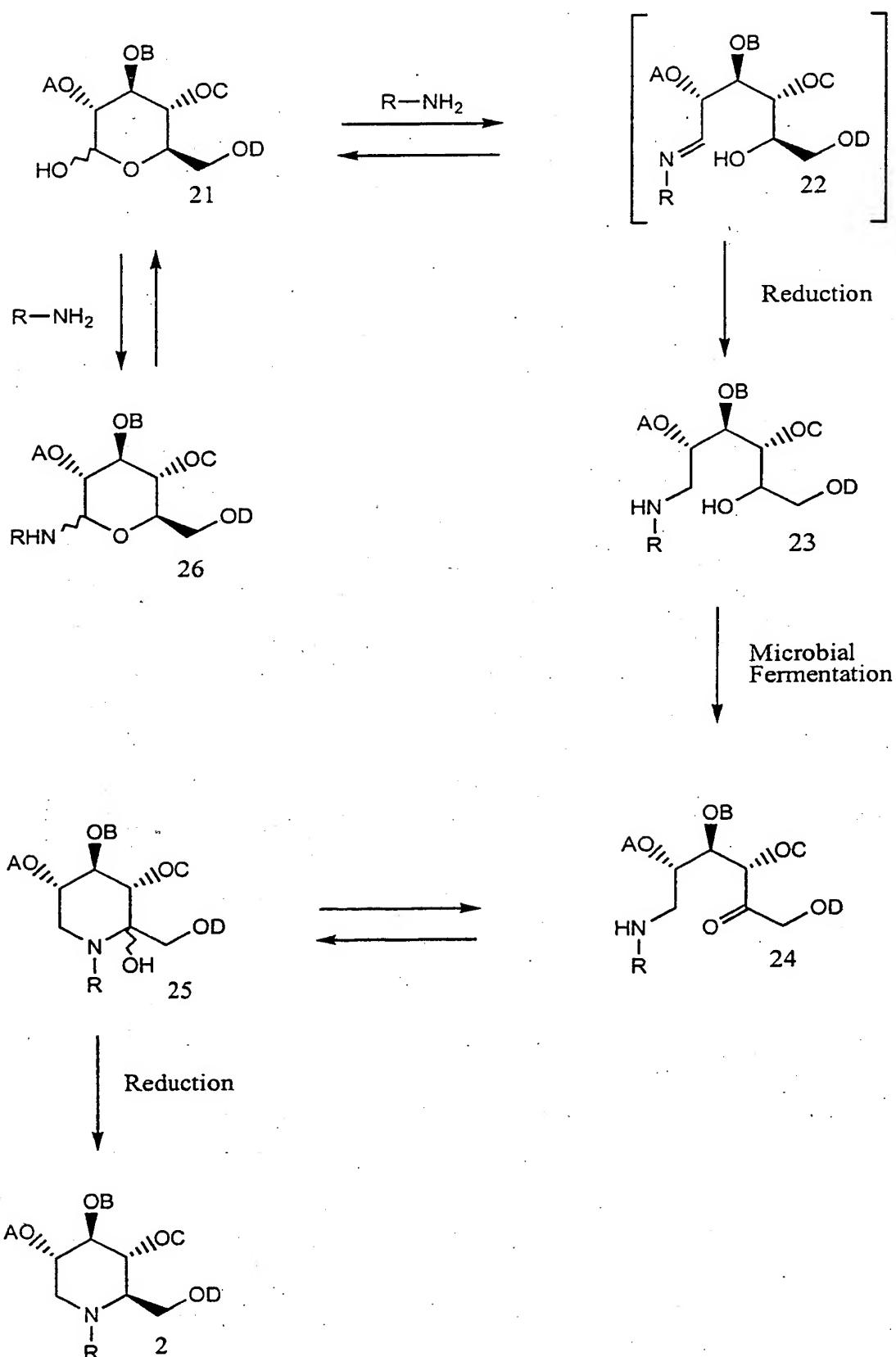
## SCHEME 3



## SCHEME 4



## SCHEME 5



Procedures are provided in the discussion and schemes that follow of exemplary chemical transformations that can be useful for the preparation of compounds of this invention. R, A, B, C and D are as defined hereinabove. P is a protecting group and L is a leaving group both of which are as defined and in the book by Green referenced below. These syntheses, as with all of the reactions discussed herein, can be carried out under a dry inert atmosphere such as a nitrogen or argon if desired. Selected reactions known to those skilled in the art, can be carried out under a dry atmosphere such as dry air whereas other synthetic steps, for example, aqueous acid or base ester or amide hydrolyses, can be carried out under ambient air.

In general, the choices of starting material and reaction conditions can vary as is well known to those skilled in the art. Usually, no single set of conditions is limiting because variations can be applied as required and selected by one skilled in the art. Conditions will also will be selected as desired to suit a specific purpose such as small scale preparations or large scale preparations. In either case, the use of less safe or less environmentally sound materials or reagents will usually be minimized. Examples of such less desirable materials are diazomethane, diethyl ether, heavy metal salts, dimethyl sulfide, some halogenated solvents, benzene and the like. In addition, many starting materials can be obtained from commercial sources from catalogs or through other arrangements.

Reaction media can be comprised of a single solvent, mixed solvents of the same or different classes or serve as a reagent in a single or mixed solvent system. The solvents can be protic, non-protic or dipolar aprotic. Non-limiting examples of protic solvents include water, methanol (MeOH), denatured or pure 95% or absolute ethanol, isopropanol and the like.

Typical non-protic solvents include acetone, tetrahydrofuran (THF), dioxane, diethylether, tert-

butylmethyl ether (TBME), aromatics such as xylene, toluene, or benzene, ethyl acetate, methyl acetate, butyl acetate, trichloroethane, methylene chloride, ethylenedichloride (EDC), hexane, heptane, isooctane, cyclohexane and the like.

5        Dipolar aprotic solvents include compounds such as dimethylformamide (DMF), dimethylacetamide (DMAc), acetonitrile, nitromethane, tetramethylurea, N-methylpyrrolidone and the like.

10        Non-limiting examples of reagents that can be used as solvents or as part of a mixed solvent system include organic or inorganic mono- or multi-protic acids or bases such as hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, formic acid, citric acid, succinic acid, triethylamine, morpholine, N-methylmorpholine, piperidine, 15        pyrazine, piperazine, pyridine, potassium hydroxide, sodium hydroxide, alcohols or amines for making esters or amides or thiols for making the products of this invention.

Room temperature or less or moderate warming ( $-10^{\circ}\text{C}$  to  $60^{\circ}\text{C}$ ) are the preferred temperatures of the synthesis and/or 20        transformations of the compounds of this invention. If desired, the reaction temperature can range from about  $-78^{\circ}\text{C}$  to the reflux point of the reaction solvent or solvents. Colder temperatures such as that of liquid nitrogen may be desired on occasion especially if improved selectivity is 25        required. Higher temperatures may also be used preferably in a pressure container system, i.e., a pressure bomb.

Examples of bases that can be used include, for example, metal hydroxides such as sodium, potassium, lithium or magnesium hydroxide, oxides such as those of sodium, 30        potassium, lithium, calcium or magnesium, metal carbonates such as those of sodium, potassium, lithium, calcium or magnesium, metal bicarbonates such as sodium bicarbonate or potassium bicarbonate, primary ( $\text{I}^{\circ}$ ), secondary ( $\text{II}^{\circ}$ ) or tertiary ( $\text{III}^{\circ}$ ) organic amines such as alkyl amines, 35        arylalkyl amines, alkylarylalkyl amines, heterocyclic amines or heteroaryl amines, ammonium hydroxides or quaternary

ammonium hydroxides. As non-limiting examples, such amines can include triethyl amine, trimethyl amine, diisopropyl amine, methyldiisopropyl amine, diazabicyclononane, tribenzyl amine, dimethylbenzyl amine, morpholine, N-methylmorpholine, N,N'-dimethylpiperazine, N-ethylpiperidine, 1,1,5,5-tetramethylpiperidine, dimethylaminopyridine, pyridine, quinoline, tetramethylethylenediamine and the like.

Non-limiting examples of ammonium hydroxides, usually made from amines and water, can include ammonium hydroxide, triethyl ammonium hydroxide, trimethyl ammonium hydroxide, methyldiisopropyl ammonium hydroxide, tribenzyl ammonium hydroxide, dimethylbenzyl ammonium hydroxide, morpholinium hydroxide, N-methylmorpholinium hydroxide, N,N'-dimethylpiperazinium hydroxide, N-ethylpiperidinium hydroxide, and the like. As non-limiting examples, quaternary ammonium hydroxides can include tetraethyl ammonium hydroxide, tetramethyl ammonium hydroxide, dimethyldiisopropyl ammonium hydroxide, benzylmethyldiisopropyl ammonium hydroxide, methyldiazabicyclononyl ammonium hydroxide, methyltribenzyl ammonium hydroxide, N,N-dimethylmorpholinium hydroxide, N,N,N', N',-tetramethylpiperazinium hydroxide, and N-ethyl-N'-hexylpiperidinium hydroxide and the like. Metal hydrides, amide or alcoholates such as calcium hydride, sodium hydride, potassium hydride, lithium hydride, sodium methoxide, potassium tert-butoxide, calcium ethoxide, magnesium ethoxide, sodium amide, potassium diisopropyl amide and the like can also be suitable reagents. Organometallic deprotonating agents such as alkyl or aryl lithium reagents such as methyl, phenyl, butyl, iso-butyl, sec-butyl or tert-butyl lithium, sodium or potassium salts of dimethylsulfoxide, Grignard reagents such as methylmagnesium bromide or methymagnesium chloride, organocadium reagents such as dimethylcadium and the like can also serve as bases for causing salt formation or



catalyzing the reaction. Quaternary ammonium hydroxides or mixed salts are also useful for aiding phase transfer couplings or serving as phase transfer reagents. Preferred base for use in the alkylation reaction is lithium diisopropyl amide as mentioned above.

A further use of bases is for the preparation of pharmaceutically acceptable salts discussed herein. These include those listed above with metal carbonates, bicarbonates, amines, quaternary amines, hydroxides and various polymeric bases being preferred.

Acids are used in many reactions during various synthesis and for the preparation of pharmaceutical salts. The Schemes as well as this discussion illustrate the use of acid for the removal of the THP protecting group, removal of a tert-butoxy carbonyl group, amine/ester exchange and the like. Acid hydrolysis of carboxylic acid protecting groups or derivatives is well known in the art. These methods, as is well known in the art, can use acid or acidic catalysts. The acid can be mono-, di- or tri-protic organic or inorganic acids. Examples of acids include hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, formic acid, citric acid, succinic acid, hydrobromic acid, hydrofluoric acid, carbonic acid, phosphorus acid, p-toluene sulfonic acid, trifluoromethane sulfonic acid, trifluoroacetic acid, difluoroacetic acid, benzoic acid, methane sulfonic acid, benzene sulfonic acid, 2,6-dimethylbenzene sulfonic acid, trichloroacetic acid, nitrobenzoic acid, dinitrobenzoic acid, trinitrobenzoic acid, and the like. They can also be Lewis acids such as aluminum chloride, borontrifluoride, antimony pentafluoride and the like.

Salts of the compounds or intermediates of this invention are prepared in the normal manner wherein acidic compounds are reacted with bases such as those discussed above to produce metal or nitrogen containing cation salts. Basic compounds such as amines can be treated with an acid

to form an amine salt. If the acid component of the salt is a weaker acid it is preferred that the base component be a stronger base. If the base component of the salt is with a weaker base it is preferred that the acid component be a stronger acid. Thus, the salts preferably are prepared from an acid having a relatively low pKa, preferably less than about 4.5. Most preferred are salts of relatively strongly basic imino sugars with strong acids. Pharmaceutically acceptable acids and bases for forming salts are well known in the art. Salts of the iminosugars of this invention and anti-viral and anti-cancer nucleosides/nucleotides are pharmaceutically acceptable salts.

Treatment of an amine substrate such as 1, 6, 11 or 16 (see reaction schemes as set forth above) with an aldehyde or ketone under reducing conditions will produce a tertiary amine of this invention such as 2. Preferred solvents include, depending on the reducing agent, alcohols or tetrahydrofuran (THF). An inert atmosphere or dry atmosphere is used again depending upon the reactivity of the reducing agent. Hydrogen gas is the usual atmosphere for catalytic reductions. These reducing agents are well known in the art.

Reductive alkylation is carried out by adding R-CHO or a ketone to an amine such as DNJ and treating with a reducing agent such as sodium cyanoborohydride or carrying out a catalytic reduction with, for example, a metal catalyst and hydrogen gas. Such reducing agents are well known in the art and include such reagents as borane, borane:THF, borane:pyridine, lithium aluminum hydride, aluminum hydride, lithium borohydride, sodium borohydride, potassium triacetylborohydride and the like. Alternatively, reductive alkylation can be carried out under hydrogenation conditions in the presence of a metal catalyst. Catalysts, hydrogen pressures and temperatures are discussed and are well known in the art. A desirable "hydride type" reductive alkylation catalyst is borane:pyridine complex. Reductive

alkylation or hydrogenation can be carried out at atmospheric pressure and higher pressures can be used if desired. Catalysts include, for example, Pd, Pd on Carbon, Pt,  $\text{PtO}_2$  and the like. Less robust catalysts (deactivated) include such thing as Pd on  $\text{BaCO}_3$  or Pd with quinoline or/and sulfur can be used in situations wherein selectivity is desired.

Acylation of substrates 1, 6, 11 or 16, as shown in the reaction schemes set out above, can be carried out in standard fashion wherein the amine is treated with a carbonyl compound with a leaving group attached as is discussed in textbooks of organic chemistry. The leaving group is designated as "L" in the Schemes and may be different in the case of, for example, carboxylic acid derivatives,  $\text{SN}_2$  substrates and  $\text{SN}_1$  substrates and the addition-elimination process with carbonyl type compounds. Well know acylating groups including those with leaving groups include halides, anhydrides, mixed anhydrides, ketenes as well as exchangeable groups such as ester groups. Coupling with an activated ester synthesized in situ is also a useful process for preparing amides and it is discussed below. For example, compound 1, 6, 11 or 16 is treated with an acid chloride in the presence of, preferably, a tertiary amine base under an inert atmosphere at between about  $-10^\circ\text{C}$  and  $0^\circ\text{C}$ . The product of this reaction is an amide 3 or 8 of this invention. A preferred acid activating group (L) is the chloride prepared by, for example, reaction of an acid with oxalyl chloride, phosphorus trichloride and the like. These carboxylic acids can be derivatized with protecting group or hydrolyzed to the acid as required.

Compounds 3 or 8 are reduced to produce 4 or 9, respectively, as a products of this invention. The reduction is carried out using procedures and reagents as discussed hereinabove and other methods as indicated. Reduction of amides is well known in the art.

Amides such as 3, 8, 13 or 18 can be hydrolyzed if desired. Base hydrolysis or acid hydrolysis methods are well known and the choice of systems will depend upon factors determined by the chemist. For example, the presence of base labile substituents might cause a scientist to select an acid hydrolysis process. Bases that can be used are listed herein. Acids are also discussed above and hydrogen chloride, toluenesulfonic acid and trifluoroacetic acid being preferred. Acid catalyzed exchange processes are also useful for converting compound 3 or 8 into other analogs or into 1.

Compounds 1, 6, 11 or 16 are also able to be protected as is shown by the preparation of 5, 10, 15 and 20, respectively. The group P in, for example, 5, 10, 15 and 20, is a special case of R wherein the group may be useful for treating disease and also useful for the preparation of other compounds of this invention. Protecting groups, P, are well known in organic chemistry along with protection/deprotection processes. They are frequently used to control reaction sites, reaction selectivities, help with resolutions such as optical resolutions, aid in purification processes and prevent over reaction in preparation processes. It should be noted that protection of groups other than nitrogen is common in the art with non-limiting examples being hydroxyl groups, thiol groups, carbonyl groups, phosphorus groups, silicon groups and the like and that P is used to indicate protecting groups in these cases also. It should also be noted that protecting groups and protection/deprotection reaction sequences are well known in the art of natural product chemistry including sugar chemistry and amino acid/peptide chemistry. Editions of the books by Thedora Green, e.g., Green, T., Protecting Groups in Organic Chemistry, Second ed., John Wiley & Sons, New York (1991), are useful in this regard and are incorporated herein by reference.

As mentioned above, contemplated compounds can include compounds wherein a nitrogen of an amine is acylated to provide, for example, amino acid carbamates. Non-limiting examples of these carbamates are the carbobenzoxy carbonyl (Z, CBZ, benzyloxycarbonyl), iso-butoxycarbonyl and tert-butoxycarbonyl (BOC, t-BOC) compounds. The materials can be made at various stages in the synthesis based on the needs and decisions made by a person skilled in the art using methods well known in the art.

Useful synthetic techniques and reagents for the preparation of the compounds of this invention include those used in protein, peptide and amino acid synthesis, coupling and transformation chemistry. The use of the tert-butoxycarbonyl (BOC) and benzyloxycarbonyl (Z) as well as their synthesis and removal are examples of such protection or synthesis schemes. This includes, for example, active ester or mixed anhydride couplings wherein preferred bases, if required, are tertiary amines such as N-methylmorpholine. Reagents for protection of the amine group of the protected amino acids include carbobenzoxy chloride, iso-butylchloroformate, tert-butoxycarbonyl chloride, di-tert-butyl dicarbonate and the like which are reacted with the amine in non-protic or dipolar aprotic solvents such as DMF or THF or mixtures of solvents.

Removal of protecting groups on nitrogen, oxygen, sulfur or other groups such as carbamates, silyl groups, THP ethers, enol ethers, ketals, acetals, hemiacetals, hemiketals, methoxymethyl ethers, benzyl, p-methoxybenzyl, or other substituted benzyl groups, acyl or aroyl groups or diphenylmethyl (benzhydryl) or triphenylmethyl (trityl) can be carried out at different stages in the synthesis of the compounds of this invention as required by methods selected by one skilled in the art. These methods are well known in the art including the amino acid, amino acid coupling, peptide synthesis, peptide mimetic synthesis art. Removal methods can include catalytic hydrogenation, base

hydrolysis, carbonyl addition reactions, acid hydrolysis, exchange and the like. Both the preparation and removal of protecting groups, for example, carbamates, trifluoroacetate groups, benzyl groups and/or substituted arylalkyl groups is discussed in Green, T., Protecting Groups in Organic Chemistry, Second ed., John Wiley & Sons, New York (1991) as discussed above. A preferred method of removal of a BOC group is HCl gas in methylene chloride which, following normal workup, provides directly an HCl salt of an amine of this invention, i.e., an ammonium salt. A preferred method of removing a Z group is catalytic reduction.

Alkylation of amines such as 1, 6, 11 or 16 is accomplished by methods well known in the art and discussed in textbooks of organic chemistry. The process is via  $SN_2$  or  $SN_1$  displacement of a leaving group, L, on a substrate by the amine. The amine is treated in a solvent such as those discussed above like DMSO, DMF, methanol, ethanol, THF, acetone and the like. Leaving groups can include halides, sulfonic acid esters such as tosylates, mesylates, triflates, trifluoroacetates and the like. The reaction can be carried out under an inert atmosphere or dry, non-oxidative conditions. An inert atmosphere is preferred.

Scheme 2 illustrates the application of the methods discussed for the preparation of compounds wherein A, B, C and D are hydrogen. It is to be noted that the syntheses may proceed in the presence of the hydroxyl groups thus the chemist has options in selecting the compound to be synthesized as well as the synthetic route to the compound.

Scheme 3 and Scheme 4 illustrate the preparation of open chain sugars containing amines 12, 14, 17 and 19, amides 13 and 18 or protected amines 15 and 20. The reductive alkylation, hydrolysis, reduction, protection, deprotection, and alkylation processes have been discussed above. These open chain compounds are useful as intermediates for the preparation of 2 and its analogs by the methods of Scheme 5. Derivatization 15 or 20 to produce

11 or 16 illustrates that protected amines can be converted and interconverted into compounds wherein A, B, C and D are as defined herein above. For example, hydroxyl groups can be alkylated, acylated by processes discussed above and well know in the art. Treatment with an aldehyde, aldimine, ketone or ketimine under, for example, acid conditions in a non-protic or dipolar aprotic solvent, produces heterocycles such as those presented above.

Scheme 5 illustrates the use of glucose, sorbose or other open chain sugars and their derivatives in the preparation of 2. For example, glucose is reacted with a primary amine  $R-NH_2$  or a derivative of the R group in  $R-NH_2$  to produce a putative imine derivative 22. R is as defined above and preferably not connected via a carbonyl carbon. Reaction can be with or without heating and with or without a catalyst such as an acid catalyst. Removal of water during imine formation from the putative open chain aldehyde intermediate is possible if desired. Reduction using methods discussed above including metal catalyzed hydrogenations produce the open chain compound 23. Microbial fermentation of the 5-hydroxy compound 23 (sugar nomenclature) leads to ketones 24 which is in equilibrium with the carbinolamine 25. The 24-25 compounds can be novel intermediates. Reduction of the 24-25 ring-chain tautomer pair produce 2.

Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers such as enantiomers, racemates and diastereoisomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes well known in the art, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base.

Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric, natural aminoacids and camphorsulfonic acid and then

separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers.

Still another available method involves synthesis of covalent diastereoisomeric molecules, e.g., esters, amides, acetals, ketals, and the like, by reacting compounds of Formula I with an optically active acid in an activated form, a optically active diol or an optically active isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. In some cases hydrolysis to the parent optically active drug is not necessary prior to dosing the patient since the compound can behave as a prodrug. The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials.

In addition to the optical isomers or potentially optical isomers discussed above, other types of isomers are specifically intended to be included in this discussion and in this invention. Examples include cis isomers, trans isomers, E isomers, Z isomers, syn- isomers, anti- isomers, tautomers, rotamers and the like. Aryl, heterocyclo or heteroaryl tautomers, heteroatom isomers, heterocyclo or heteroaryl heteroatom isomers and ortho, meta or para substitution isomers are also included as isomers as are multicyclic isomers such as those of the phenanthrene/anthracene type and the multicyclic saturated or partially unsaturated type. The latter type of isomer is exemplified in general by bicyclo[2,2,2]octane and bicyclo[3,2,1]octane. Solvates or solvent addition compounds such as hydrates or alcoholates are also specifically included both as chemicals of this invention



and in, for example, formulations or pharmaceutical compositions for drug delivery.

Where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, e.g., a hydrocarbyl radical or a halogen, hydroxy, amino and the like functional group, is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure. For example, two hydroxyl groups, two amino groups, two thiol groups or a mixture of two hydrogen-heteroatom groups on the same carbon are known not to be stable without protection or as a derivative.

The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions can not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

Other compounds of this invention that are acids can also form salts. Examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases or basic quaternary ammonium salts.

In some cases, the salts can also be used as an aid in the isolation, purification or resolution of the compounds of this invention.

Prodrugs are drugs that can be chemically converted *in vivo* or *in vitro* by biological systems into an active drug or drugs, i.e., it is a pharmaceutically acceptable bioprecursor of a desired pharmaceutical or pharmaceuticals. The prodrug can be a compound having a structural formula different from the active compound but which upon administration to a mammal or *in vitro* system is converted into a compound of this invention. Such prodrugs are also compounds of this invention useful for the treatment of human, agricultural and general veterinary diseases.

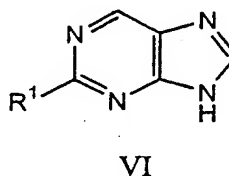
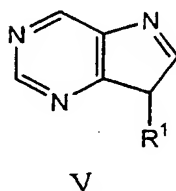
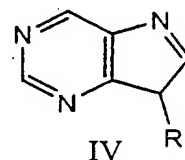
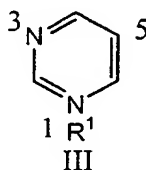
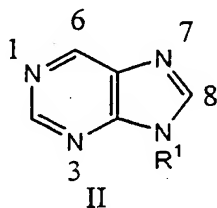
In treating hepatitis B virus or hepatitis C virus infections, one can use the present substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds alone or in combination in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, phosphate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate, and undecanoate.

The basic nitrogen-containing groups can be quaternized with agents such as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates such as dimethyl, diethyl, dibutyl, and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides; aralkyl halides such as benzyl and phenethyl bromides, and

others. Water- or oil-soluble or dispersible products are thereby obtained as desired. The salts are formed by combining the basic compounds with the desired acid.

### Nucleosides and Nucleotides

- 5 Nucleosides and nucleotides useful in the present invention are purine (II) base compounds or pyrimidine (III) base compounds, or analogs such as compounds IV, V or VI.



- Position numbering for purines and pyrimidines is as shown in structures II and III. R¹ can be selected from
- 10 hydroxyalkyl, hydroxyalkenyl, carboxyalkyl, carboxyalkenyl, thiolalkyl, alkylthioalkyl, alkoxyalkyl, alkoxyalkenyl, heterocycle, heterocyclo-alkyl, hydroxyalkylalkoxyalkyl, alkoxyalkylalkoxyalkyl, and cycloalkylalkyl. The purine compounds can be further substituted at positions 1, 2, 3,
- 15 6, 7, or 8 of the purine heterocycle, and the pyrimidine compounds can be substituted at positions 2, 3, 4, 5, or 6

of the pyrimidine heterocycle. Such substituents can be selected from hydroxy, alkoxy, halo, thiol, amino, carboxyl, mono-substituted amino, di-substituted amino, and alkyl.

The following definitions are applicable only to the structures of Formulas II, III, IV, V and VI of this invention. When used in combination with another radical when referring to the purines and pyrimidines useful in the present invention, the term "alkyl" means a straight or branched chain hydrocarbon radical containing from 1 to 8 carbon atoms, preferably 1 to 4 carbon atoms. When used in combination with another radical, the term "alkenyl" means a straight or branched chain hydrocarbon radical having 1 or more double bonds, containing from 2 to 8 carbon atoms, preferably 1 to 4 carbon atoms. When used alone when referring to purines and pyrimidines useful in the present invention, the term "alkyl" means a straight or branched chain alkyl radical containing from six to 14 carbon atoms, preferably seven to 12 carbon atoms, and most preferably eight to 11 carbon atoms. The term "aryl" alone or in combination with another radical means a phenyl, naphthyl, or indenyl ring, optionally substituted with one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, or nitro. "Alkanoyl" means branched or straight chain alkanecarbonyl having a chain length of  $C_1$  to  $C_{20}$ , preferably  $C_2$  to  $C_{14}$ , more preferably  $C_4$  to  $C_{10}$ ; "aroyl" means arylcarbonyl; and "trifluoroalkanoyl" means alkyl containing three fluoro substituents. "Halogen" means fluorine, chlorine, bromine, or iodine. "Thiol" means sulfur substituted with hydrogen (-SH). "Amino" means nitrogen with two hydrogen atoms; "monosubstituted amino" and "disubstituted amino" mean amino groups further independently substituted with one or more alkyl or arylalkyl groups. "Hydroxyalkyl" means an alkyl group substituted with one or more hydroxyl groups; "hydroxy-alkenyl" means an alkenyl group substituted with one or more hydroxyl groups; "thioalkyl" means an alkyl substituted with

one or more thiol (SH) groups; "alkoxyalkyl" means an alkyl substituted with one or more alkyl ether groups;

"alkoxyalkenyl" means an alkenyl group substituted with one

or more alkyl ether groups; "hydroxyalkylalkoxyalkyl" means

5 an alkoxyalkyl group substituted with a hydroxyalkyl group;

"alkoxyalkyl-alkoxyalkyl" means an alkoxyalkyl group

substituted with an alkoxyalkyl group; "cycloalkylalkyl"

means an alkyl group substituted with a cycloalkyl group.

The term "heterocycle," alone or in combination, means a

10 saturated or partially unsaturated 5 or 6-membered ring

containing one or more oxygen, nitrogen, and/or sulfur

heteroatoms. Said heterocycle can further be substituted

with one to four substituents, which can be independently, hydroxy, hydroxyalkyl, thiol, alkoxy, azido, nitro, a

15 halogen atom, amino, mono-substituted amino, or

disubstituted amino. Heterocycloalkyl means an alkyl group

wherein one or more hydrogen atoms are replaced by a

substituted or unsubstituted heterocyclic ring.

Also included are the tautomers of the substituents on

20 the compounds of the invention. Non-limiting examples of

tautomers are ketone/enol tautomers, imino/amino tautomers,

N-substituted imino/N-substituted amino tautomers,

thiol/thiacarbonyl tautomers, and ring-chain tautomers such

as the five and six membered ring oxygen, nitrogen, sulfur,

25 or oxygen- and sulfur- containing heterocycles also

containing substituents alpha to the heteroatoms. Also

specifically included in the present invention are

enantiomers and diastereomers, as well as racemates and

isomeric mixtures of the compounds discussed herein.

30 Representative nucleoside and nucleotide compounds

useful in the present invention include, but are not limited to:

(+)-cis-5-fluoro-1-[2-(hydroxy-methyl)-[1,3-oxathiolan -5-yl]cytosine;

35 (-)-2'-deoxy-3'-thiocytidine-5'-triphosphate (3TC);

- (-)-cis-5-fluoro-1-[2-(hydroxy-methyl)-[1,3-oxathiolan-5-yl]cytosine (FTC);
- (-)-2',3', dideoxy-3'-thiacytidine [(-)-SddC];
- 1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)-5-iodocytosine (FIAC);
- 1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)-5-iodocytosine triphosphate (FIACTP);
- 1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)-5-methyluracil (FMAU);
- 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide; 2',3'-dideoxy-3'-fluoro-5-methyl-dexocytidine (FddMeCyt);
- 2',3'-dideoxy-3'-chloro-5-methyl-dexocytidine (ClddMeCyt);
- 2',3'-dideoxy-3'-amino-5-methyl-dexocytidine (AddMeCyt);
- 2',3'-dideoxy-3'-fluoro-5-methyl-cytidine (FddMeCyt);
- 2',3'-dideoxy-3'-chloro-5-methyl-cytidine (ClddMeCyt);
- 2',3'-dideoxy-3'-amino-5-methyl-cytidine (AddMeCyt);
- 2',3'-dideoxy-3'-fluorothymidine (FddThd);
- 2',3'-dideoxy-beta-L-5-fluorocytidine (beta-L-FddC);
- 2',3'-dideoxy-beta-L-5-thiacytidine;
- 2',3'-dideoxy-beta-L-5-cytidine (beta-L-ddC);
- 9-(1,3-dihydroxy-2-propoxymethyl)guanine;
- 2'-deoxy-3'-thia-5-fluorocytosine;
- 3'-amino-5-methyl-dexocytidine (AddMeCyt);
- 2-amino-1,9-[(2-hydroxymethyl-1-(hydroxymethyl)ethoxy)methyl]-6H-purin-6-one (ganciclovir);
- 2-[2-(2-amino-9H-purin-9y)ethyl]-1,3-propandiol diacetate (famciclovir);
- 2-amino-1,9-dihydro-9-[(2-hydroxy-ethoxy)methyl]6H-purin-6-one (acyclovir);
- 9-(4-hydroxy-3-hydroxymethyl-but-1-yl)guanine (penciclovir);
- 9-(4-hydroxy-3-hydroxymethyl-but-1-yl)-6-deoxy-guanine, diacetate (famciclovir);

3'-azido-3'-deoxythymidine (AZT);  
3'-chloro-5-methyl-dexocytidine (ClddMeCyt);  
9-(2-phosphonyl-methoxyethyl)-2',6'-diaminopurine-2',3'-dideoxyriboside;  
5 9-(2-phosphonylmethoxyethyl)adenine (PMEA);  
acyclovir triphosphate (ACVTP);  
D-carbocyclic-2'-deoxyguanosine (CdG);  
dideoxy-cytidine;  
dideoxy-cytosine (ddC);  
10 dideoxy-guanine (ddG);  
dideoxy-inosine (ddI);  
E-5-(2-bromovinyl)-2'-deoxyuridine triphosphate;  
fluoro-arabinofuranosyl-iodouracil;  
1-(2'-deoxy-2'-fluoro-1-beta-D-arabinofuranosyl)-5-iod  
15 o-uracil (FIAU);  
stavudine;  
9-beta-D-arabinofuranosyl-9H-purine-6-amine monohydrate  
(Ara-A);  
9-beta-D-arabinofuranosyl-9H-purine-6-amine-5'-monopho  
20 sphate monohydrate (Ara-AMP);  
2-deoxy-3'-thia-5-fluorocytidine;  
2',3'-dideoxy-guanine; and  
2',3'-dideoxy-guanosine.  
A preferred compound is (-)-2'-deoxy-3'-thiocytidine-  
25 5'-triphosphate (3TC).

Synthetic methods for the preparation of nucleosides and nucleotides useful in the present invention are likewise well known in the art as disclosed in Acta Biochim. Pol., 43, 25-36 (1996); Swed. Nucleosides Nucleotides 15, 361-378 (1996), Synthesis 12, 1465-1479 (1995), Carbohydr. Chem. 27, 242-276 (1995), Chem. Nucleosides Nucleotides 3, 421-535 (1994), Ann. Reports in Med. Chem., Academic Press; and Exp. Opin. Invest. Drugs 4, 95-115 (1995).

The chemical reactions described in the references  
35 cited above are generally disclosed in terms of their broadest application to the preparation of the compounds of

this invention. Occasionally, the reactions may not be applicable as described to each compound included within the scope of compounds disclosed herein. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

While nucleoside analogs are generally employed as antiviral agents as is, nucleotides (nucleoside phosphates) must sometimes have to be converted to nucleosides in order to facilitate their transport across cell membranes. An example of a chemically modified nucleotide capable of entering cells is S-1-3-hydroxy-2-phosphonylmethoxypropyl cytosine (HPMPC, Gilead Sciences).

Nucleoside and nucleotide compounds of this invention that are acids can form salts. Examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium, or magnesium, or with organic bases or basic quaternary ammonium salts.

#### Immunomodulators and Immunostimulants

A large number of immunomodulators and immunostimulants that can be used in the methods of the present invention are currently available. A list of these compounds is provided in Table 1, below.



## TABLE 1

	AA-2G
	adamantylamide dipeptide
	adenosine deaminase, Enzon
5	adjuvant, Alliance
	adjuvants, Ribl
	adjuvants, Vaxcel
	Adjuvax
	agelasphin-11
10	AIDS therapy, Chiron
	algal glucan, SRI
	algammulin, Anutech
	Anginlyc
	anticellular factors, Yeda
15	Anticort
	antigastrin-17 immunogen, Ap
	antigen delivery system, Vac
	antigen formulation, IDBC
	antiGnRH immunogen, Aphton
20	Antiherpin
	Arbidol
	azarole
	Bay-q-8939
	Bay-r-1005
25	BCH-1393
	Betafectin
	Biostim
	BL-001
	BL-009
30	Broncostat
	Cantastim
	CDRI-84-246
	cefodizime
	chemokine inhibitors, ICOS
35	CMV peptides, City of Hope

	CN-5888
	cytokine-releasing agent, St
	DHEAS, Paradigm
	DISC TA-HSV
5	J07B
	I01A
	I01Z
	ditiocarb sodium
	ECA-10-142
10	ELS-1
	endotoxin, Novartis
	FCE-20696
	FCE-24089
	FCE-24578
15	FLT-3 ligand, Immunex
	FR-900483
	FR-900494
	FR-901235
	FTS-Zn
20	G-proteins, Cadus
	gludapcin
	glutaurine
	glycophosphopeptical
	GM-2
25	GM-53
	GMDP
	growth factor vaccine, Entrem
	H-BIG, NABI
	H-CIG, NABI
30	HAB-439
	Helicobacter pylori vaccine,
	herpes-specific immune factor
	HIV therapy, United Biomed
	HyperGAM+CF
35	ImmuMax
	Immun BCG

immune therapy, Connective  
immunomodulator, Evans  
immunomodulators, Novacell  
imreg-1  
5 imreg-2  
Indomune  
inosine pranobex  
interferon, Dong-A (alpha2)  
interferon, Genentech (gamma)  
10 interferon, Novartis (alpha)  
interleukin-12, Genetics Ins  
interleukin-15, Immunex  
interleukin-16, Research Cor  
ISCAR-1  
15 J005X  
L-644257  
licomarasminic acid  
LipoTher  
LK-409  
20 LK-410  
LP-2307  
LT(R1926)  
LW-50020  
MAF, Shionogi  
25 MDP derivatives, Merck  
met-enkephalin, TNI  
methylfurylbutyrolactones  
MIMP  
mirimostim  
30 mixed bacterial vaccine, Tem  
MM-1  
moniliastat  
MPLA, Rib  
MS-705  
35 murabutide  
murabutide, Vacsyn

muramyl dipeptide derivative  
muramyl peptide derivatives  
myelopid  
-563  
5 NACOS-6  
NH-765  
NISV, Proteus  
NPT-16416  
NT-002  
10 PA-485  
PEFA-814  
peptides, Scios  
peptidoglycan, Pliva  
Perthon, Advanced Plant  
15 PGM derivative, Pliva  
Pharmaprojects No. 1099  
Pharmaprojects No. 1426  
Pharmaprojects No. 1549  
Pharmaprojects No. 1585  
20 Pharmaprojects No. 1607  
Pharmaprojects No. 1710  
Pharmaprojects No. 1779  
Pharmaprojects No. 2002  
Pharmaprojects No. 2060  
25 Pharmaprojects No. 2795  
Pharmaprojects No. 3088  
Pharmaprojects No. 3111  
Pharmaprojects No. 3345  
Pharmaprojects No. 3467  
30 Pharmaprojects No. 3668  
Pharmaprojects No. 3998  
Pharmaprojects No. 3999  
Pharmaprojects No. 4089  
Pharmaprojects No. 4188  
35 Pharmaprojects No. 4451  
Pharmaprojects No. 4500

	Pharmaprojects No. 4689
	Pharmaprojects No. 4833
	Pharmaprojects No. 494
	Pharmaprojects No. 5217
5	Pharmaprojects No. 530
	pidotimod
	pimelautide
	pinafide
	PMD-589
10	podophyllotoxin, Conpharm
	POL-509
	poly-ICLC
	poly-ICLC, Yamasa Shoyu
	PolyA-PolyU
15	Polysaccharide A
	protein A, Berlox Bioscience
	PS34WO
	pseudomonas MAbs, Teijin
	Psomaglobin
20	PTL-78419
	Pyrexol
	pyriferone
	Retrogen
	Retropep
25	RG-003
	Rhinostat
	rifamaxil
	RM-06
	Rollin
30	romurtide
	RU-40555
	RU-41821
	rubella antibodies, ResCo
	S-27609
35	SB-73
	SDZ-280-636

88

	SDZ-MRL-953
	SK&F-107647
	SL04
	SL05
5	SM-4333
	Solutein
	SRI-62-834
	SRL-172
	ST-570
10	ST-789
	staphage lysate
	Stimulon
	suppressin
	T-150R1
15	T-LCEF
	tabilautide
	temurtide
	Theradigm-HBV
	Theradigm-HPV
20	Theradigm-HSV
	THF, Pharm & Upjohn
	THF, Yeda
	thymalfasin
	thymic hormone fractions
25	thymocartin
	thymolymphtropin
	thymopentin
	thymopentin analogues
	thymopentin, Peptech
30	thymosin fraction 5, Alpha
	thymostimulin
	thymotrinan
	TMD-232
	TO-115
35	transfer factor, Viragen
	tuftsin, Selavo

89

	ubenimex
	Ulsastat
	ANGG-
	CD-4+
5	Collag+
	COLSF+
	COM+
	DA-A+
	GAST-
10	GF-TH+
	GP-120-
	IF+
	IF-A+
	IF-A-2+
15	IF-B+
	IF-G+
	IF-G-1B+
	IL-2+
	IL-12+
20	IL-15+
	IM+
	LHRH-
	LIPCOR+
	LYM-B+
25	LYM-NK+
	LYM-T+
	OPI+
	PEP+
	PHG-MA+
30	RNA-SYN-
	SY-CW-
	TH-A-1+
	TH-5+
	TNF+
35	UN

Dosages

The substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds useful in the present invention can be administered to humans in an amount in the range of from about 0.1 mg/kg/day to about 100 mg/kg/day, more preferably from about 1 mg/kg/day to about 75 mg/kg/day, and most preferably from about 5 mg/kg/day to about 50 mg/kg/day..

The nucleoside or nucleotide antiviral compound, or mixtures thereof, can be administered to humans in an amount in the range of from about 0.1 mg/person/day to about 500 mg/person/day, preferably from about 10 mg/person/day to about 300 mg/person/day, more preferably from about 25 mg/person/day to about 200 mg/person/day, even more preferably from about 50 mg/person/day to about 150 mg/person/day, and most preferably in the range of from about 1 mg/person/day to about 50 mg/person/day.

Immunomodulators and immunostimulants useful in the present invention can be administered in amounts lower than those conventional in the art. For example, thymosin alpha 1 and thymosin fraction 5 are typically administered to humans for the treatment of HepB infections in an amount of about 900 g/m<sup>2</sup>, two times per week (Hepatology (1988) 8:1270; Hepatology (1989) 10:575; Hepatology (1991) 14:409; Gastroenterology (1995) 108:A1127). In the methods and compositions of the present invention, this dose can be in the range of from about 10 g/m<sup>2</sup>, two times per week to about 750 g/m<sup>2</sup>, two times per week, more preferably from about 100 g/m<sup>2</sup>, two times per week to about 600 g/m<sup>2</sup>, two times per week, most preferably from about 200 g/m<sup>2</sup>, two times per week to about 400 g/m<sup>2</sup>, two times per week. Interferon alfa is typically administered to humans for the treatment of HepC infections in an amount of from about 1 X 10<sup>6</sup> units/person, three times per week to about 10 X 10<sup>6</sup> units/person, three times per week (Simon et al., (1997) Hepatology 25:445-448). In the methods and compositions of the present invention, this dose can be in the range of from



about  $0.1 \times 10^6$  units/person, three times per week to about  $7.5 \times 10^6$  units/person, three times per week, more preferably from about  $0.5 \times 10^6$  units/person, three times per week to about  $5 \times 10^6$  units/person, three times per week, most preferably from about  $1 \times 10^6$  units/person, three times per week to about  $3 \times 10^6$  units/person, three times per week.

Due to the enhanced hepatitis virus antiviral effectiveness of these immunomodulators and immunostimulants in the presence of the N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds useful in the present invention, reduced amounts of other immunomodulators/immunostimulants can be employed in the methods and compositions disclosed herein. Such reduced amounts can be determined by routine monitoring of hepatitis virus in infected patients undergoing therapy. This can be carried out by, for example, monitoring hepatitis viral DNA in patients' serum by slot-blot, dot-blot, or PCR techniques, or by measurement of hepatitis surface or other antigens, such as the e antigen, in serum. Methods therefor are discussed in Hoofnagle et al., (1997) New Engl. Jour. Med. 336(5):347-356, and F.B. Hollinger in Fields Virology, Third Ed., Vol. 2 (1996), Bernard N. Fields et al., Eds., Chapter 86, "Hepatitis B Virus," pp. 2738-2807, Lippincott-Raven, Philadelphia, PA, and the references cited therein.

Patients can be similarly monitored during combination therapy employing N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds and nucleoside and/or nucleotide antiviral agents to determine the lowest effective doses of each.

The doses described above can be administered to a patient in a single dose or in proportionate multiple subdoses. In the latter case, dosage unit compositions can contain such amounts of submultiples thereof to make up the daily dose. Multiple doses per day can also increase the

total daily dose should this be desired by the person prescribing the drug.

### Pharmaceutical Compositions

The compounds of the present invention can be formulated as pharmaceutical compositions. Such compositions can be administered orally, parenterally, by inhalation spray, rectally, intradermally, transdermally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania (1975), and Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y. (1980).

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are useful in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, and

polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

Suppositories for rectal administration of the compounds discussed herein can be prepared by mixing the active agent with a suitable non-irritating excipient such as cocoa butter, synthetic mono-, di-, or triglycerides, fatty acids, or polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature, and which will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral

administration. The compounds can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form will vary depending upon the patient and the particular mode of administration.

Certain of the pharmaceutical compounds of this invention which are administered in accordance with the methods of the invention can serve as prodrugs to other compounds of this invention. Prodrugs are drugs that can be chemically converted in vivo or in vitro by biological systems into an active derivative or derivatives. Prodrugs are administered in essentially the same fashion as the other pharmaceutical compounds of the invention. Non-limiting examples are the esters of the N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds of this invention.

Compounds of the combinations of this invention, for example N-(n-nonyl)-1,5-dideoxy-1,5-imino-D-glucitol and various nucleosides or nucleotides, may be acids or bases. As such, they may be used to form salts with one another. Nucleosides are purine or pyrimidine compounds lacking a phosphate ester. Compounds of Formulas II, III, IV, V, or VI herein without a phosphate ester but containing a carboxylic acid moiety could form a salt with an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of the

present invention. Nucleotides are purine or pyrimidine compounds that are mono-, di-, or triphosphate esters. These phosphate esters contain free -OH groups that are acidic, and that can form salts with inorganic bases or organic bases. Salt formation with organic bases depends on the pKa of the acid and base. Certain N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds disclosed herein are basic and form pharmaceutically acceptable ammonium or quaternary ammonium salts. In the present case, useful salts can be formed not only with pharmaceutically acceptable acids, but also with biologically active acids such as the nucleosides and nucleotides disclosed herein. These salts can be prepared in the conventional manner for preparing salts, as is well known in the art. For example, one can treat the free base of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound with a nucleotide analog of Formula II, III, IV, V, or VI to form a salt. This can be performed as a separate chemical reaction, or as part of the formulation process. The limiting reagent in the salt forming reaction is either the acid or base, as selected by the artisan to obtain a suitable biological result. The formulation can contain mixtures of different salts, acids, or free bases as desired. For example, the phosphoric acid form of (-)-2'-deoxy-3'-thiocytidine-5'-triphosphate will form a salt with the base form of N-(n-nonyl)-1,5-dideoxy-1,5-imino-D-glucitol or N-(n-nonyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrates. This type of salt can then be provided to the patient in a pharmaceutically acceptable formulation, as a pure single salt, or as part of a mixture. These acids and bases can be independently formulated and maintained in separate compartments in the same formulation if desired.

In some cases, the salts can also be used as an aid in the isolation, purification, or resolution of the compounds of this invention.

### Treatment Regimen

The regimen for treating a patient suffering from a hepatitis virus infection with the compounds and/or compositions of the present invention is selected in accordance with a variety of factors, including the age, weight, sex, diet, and medical condition of the patient, the severity of the infection, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic, and toxicology profiles of the particular compounds employed, and whether a drug delivery system is utilized.

Administration of the drug combinations disclosed herein should generally be continued over a period of several weeks to several months or years until virus titers reach acceptable levels, indicating that infection has been controlled or eradicated. As noted above, patients undergoing treatment with the drug combinations disclosed herein can be routinely monitored by measuring hepatitis viral DNA in patients' serum by slot-blot, dot-blot, or PCR techniques, or by measurement of hepatitis antigens, such as hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg), in serum to determine the effectiveness of therapy. In chronic hepatitis B, for example, remissions are characterized by the disappearance of hepatitis B viral DNA, i.e., reduction to undetectable levels as measured by hybridization tests capable of detecting levels  $10^5$  genomes per ml of serum, and HBeAg from serum despite the continued presence of HBsAg. These serologic events are followed by improvement in the biochemical and histologic features of the disease. The end point of successful treatment in most trials of antiviral therapy is the disappearance of HBeAg and viral DNA from serum. In patients in whom the e antigen disappears, remission is usually sustained, and results in an inactive HBsAg carrier state. Many patients eventually become HBsAg-negative (see Hoofnagle et al., (1997) New Engl. Jour. Med. 336(5):347-356 for a review).

Continuous analysis of the data obtained by these methods permits modification of the treatment regimen during therapy so that optimal amounts of each component in the combination are administered, and so that the duration of treatment can be determined as well. Thus, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amounts of each of the antiviral compounds used in combination which together exhibit satisfactory anti-hepatitis virus effectiveness are administered, and so that administration of such antiviral compounds in combination is continued only so long as is necessary to successfully treat the infection.

The following non-limiting examples serve to illustrate various aspects of the present invention.

15

#### Example 1

##### Preparation of

##### 1,5-(butylimino)-1,5-dideoxy-D-glucitol

A solution of 1,5-dideoxy-1,5-imino-D-glucitol (5.14 g, 0.0315 mole), butyraldehyde (3.35 ml, 0.0380 mole) and Pd black (1 g) in 200 ml methanol was hydrogenated (60 psi/29C/21 hrs.). After filtering the resulting mixture, the filtrate was concentrated in vacuo to an oil. The title compound was crystallized from acetone, and recrystallized from methanol/acetone, m.p. ca. 132C. The structure assignment was supported by NMR, infrared spectra and elemental analysis.

25

Analysis calcd. for  $C_{10}H_{21}NO_4$ : C, 54.78; H, 9.65; N, 6.39. Found: C, 54.46; H, 9.33; N, 6.46.

30

#### Example 2

##### Preparation of

##### 1,5-(butylimino)-1,5-dideoxy-D-glucitol, tetraacetate

Acetic anhydride (1.08 g, 0.0106 mole) was added to the title compound of Example 1 (0.50 g, 0.0023 mole) in 5 ml pyridine and stirred for 17 days at room temperature. The

35

product was evaporated under nitrogen gas. The resulting title compound was purified by silica gel chromatography. Structure assignment was supported by NMR, infrared spectra and elemental analysis.

5            Analysis calcd. for  $C_{18}H_{29}NO_9$ : C, 55.80; H, 7.54; N, 3.62. Found: C, 55.42; H, 7.50; N, 3.72.

### Example 3

Anti-Hepatitis B Virus Activity of Various  
N-Substituted-1,5-Dideoxy-1,5-Imino-D-Glucitol Compounds

10 In Vitro

The anti-hepatitis B virus activity and effect on cell viability of a number of different N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds were assessed using an in vitro assay employing chronically hepatitis B virus secreting HepG2.2.15 cells. The method employed was essentially that described in Block et al. (1994) Proc. Natl. Acad. Sci. USA 91:2235-2239. The results are shown in Tables 2 and 3.

TABLE 2

20      Effect of N-Substituted-1,5-Dideoxy-1,5-Imino-D-Glucitol  
Compounds on Hepatitis B Virus Secretion and Viability of  
HepG2.2.15 Cells

	Compound and of [Concentration] <sup>1</sup> As A %	% Viable +/-1 S.D. <sup>2,5</sup> of Control <sup>3</sup>	Relative amount HBV secreted
25	Control	90 +/-7 (n=4)	100
	NBDNJ [200]	94 +/-6 (n=10)	37.0 +/-13 (n=15)
30	NBDNJ [1000]	88 +/-8 (n=10)	3.2 +/-5 (n=15)
	1 [200]	90 +/-2 (n=4)	85.0 +/-5 (n=8)



	1	[1000]	87 +/-3 (n=4)	35.0 +/-6 (n=8)
	2	[200]	90 +/-6 (n=4)	107.0 +/-12 (n=3)
	2	[1000]	89 +/-4 (n=4)	38.0 +/-15 (n=3)
	3	[200]	n.d. <sup>4</sup>	45.0 +/-30 (n=3)
5	3	[1000]	n.d. <sup>4</sup>	5.0 +/-20 (n=3)
	4	[200]	93 +/-1 (n=4)	60.0 (n=2)
	4	[1000]	91 +/-3 (n=4)	34.0 (n=2)
	5	[200]	88 +/-6 (n=4)	0.0 +/-0 (n=3)
	5	[1000]	5 +/-5 (n=4)	0.0 +/-0 (n=3)
10	6	[200]	n.d.	58.0 +/-20 (n=3)
	6	[1000]	n.d.	20.0 +/-15 (n=3)

<sup>4</sup>Chronically HBV secreting 2.2.15 cells (approximately 500,000 per well) were incubated in the presence of indicated compound for three days.

15 <sup>2</sup>After 3 days of culture in the absence or presence of compound, cells were removed by trypsin treatment, incubated with trypan blue, and visually examined for dye exclusion by microscopy. Values are the percentage, relative to the total number of cells examined, of cells excluding trypan  
20 blue (trypan blue exclusion was considered equivalent to viability).

<sup>3</sup>After 3 days of incubation in the absence or presence of compound, secreted virions were immunoprecipitated from the culture medium with monoclonal antibody specific for preS1  
25 antigen (Meisel et al. (1995) Intervirology 37:330-339; Lu et al. (1995) Virology 213:660-665). Viral DNA present in the immunoprecipitates was detected by densitometric quantification of the DNA fragment of the correct size resulting from a polymerase chain reaction. The amount of  
30 DNA amplified from control (cells receiving no compound) is assumed to be 100%.

NBDNJ: N-(n-butyl)-1,5-dideoxy-1,5-imino-D-glucitol; N-butyl DNJ.

Although trypan blue viability staining was not performed, cells appeared unremarkable (healthy) by gross microscopic examination.

<sup>5</sup>S.D.: standard deviation.

5 Compounds:

- 1: N-(3-phenylpropyl)-1,5-dideoxy-1,5-imino-D-glucitol
- 2: N-(n-butyl)-1,5-dideoxy-1,5-imino-D-glucitol,  
tetrabutyrates
- 3: N-(2-ethylbutyl)-1,5-dideoxy-1,5-imino-D-glucitol
- 10 4: N-(4,4,4-trifluorobutyl)-1,5-dideoxy-1,5-imino-D-glucitol
- 5: N-(8,8,8-trifluorooctyl)-1,5-dideoxy-1,5-imino-D-glucitol
- 15 6: N-(6,6,6-trifluorohexyl)-1,5-dideoxy-1,5-imino-D-glucitol

TABLE 3

Effect of N-Substituted-1,5-Dideoxy-1,5-Imino-D-Glucitol Compounds on Hepatitis B Virus Secretion and Viability of HepG2.2.15 Cells

20	Compound	[I] for 90% HBV secretion inhibition <sup>1</sup>	[I] for a 50% reduction in MMT <sup>2</sup>
	1	0.5-1.0*	100-200
	2	>200*s*	ND
25	3	200*	>200
	4	200*	>200
	5	200*	>200
	6	>200**	>200
	7	>200**	>200
30	8	>200**	>200
	9	>200**	>200
	10	-200	500

<sup>1</sup>in microgs per ml. and based upon duplicate PCR results.

<sup>2</sup>in microgs per ml.; MTT:

<sup>3</sup>Not determined.

5   <sup>4</sup>lowest concentration tested.

\*\*there was no inhibition seen at the highest concentration used (200 microgs/ml).

Compounds:

- 1: N-(n-nonyl)-1,5-dideoxy-1,5-imino-D-glucitol
- 10   2: N-(n-butyl)-1,5-dideoxy-1,5-imino-D-glucitol, diacetate
- 3: 1,5-dideoxy-1,5-imino-D-glucitol, tetracetate
- 4: N,O-(1,6-carbonyl)-1,5-dideoxy-1,5-imino-D-glucitol
- 5: N-(n-butyl)-2,3-dimethoxy-1,5-dideoxy-1,5-imino-D-glucitol
- 15   6: N-(n-hexyl)-4,6-benzylidene-1,5-dideoxy-1,5-imino-D-glucitol
- 7: N-(n-butyl)-3-methoxy-1,5-dideoxy-1,5-imino-D-glucitol
- 8: N-(4,4,4-trifluorobutyl)-2,3-dimethoxy-1,5-dideoxy-1,5-imino-D-glucitol, tetracetate
- 20   9: N,O-(1,6-methylenecarbonyl)-1,5-dideoxy-1,5-imino-D-glucitol
- 10: N-(8,8,8-trifluorooctyl)-1,5-dideoxy-1,5-imino-D-glucitol

MMT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium  
25   bromide.

The MTT-based colorimetric assay is a measurement of cell viability (Heo et al. (1990) Cancer Research 50:3681-3690).

#### Example 4

Anti-Hepatitis B Virus Activity of  
30   (-)-2'-deoxy-3'-thiocytidine-5'-triphosphate (3TC)  
Alone and in Combination with N-nonyl-DNJ

The anti-hepatitis B virus effect of (-)-2'-deoxy-3'-thiocytidine-5'-triphosphate (3TC) alone and in combination with N-nonyl-DNJ was determined according to Korba ((1996)

Antiviral Research 29(1):49-51), using the "combostat" strategy (Comstat Program, Combostat Corp., Duluth, MN). The combostat method involves serially diluting the IC-90 of each compound. The IC-90 of N-nonyl-DNJ has been determined to be between 4 and 10 g/ml (T. Block and G. Jacob, unpublished observation). The accepted IC-90 for 3TC in HepG 2.2.15 (2.2.15) cells is 300nM to 500nM (Doong et al. (1991) Proc. Natl. Acad. Sci. USA 88:8495-8499).

2.2.15 cells, described in Sells et al. (1987) Proc. Natl. Acad. Sci. USA 84:1005-1009, were maintained in RPMI 1640 medium (Gibco BRL, #31800-022) supplemented with 10% fetal bovine serum, 200 g/ml G418 (Gibco BRL 066-1811). Cells were seeded into 25 cm<sup>2</sup> flasks at 80% confluency. Five days later, flasks in triplicate received either no compound, serial dilutions of 3TC alone, or serial dilutions of 3TC plus N-nonyl-DNJ. At 2, 4, and 6 days after addition of compound (with medium replacement on those days), the amount of hepatitis B virus (HBV) DNA in the culture medium was determined by PCR analysis of polyethyleneglycol-sedimented particles. Thus, in these experiments, enveloped particles were not distinguished from nucleocapsids. PCR-amplified products were resolved by agarose gel electrophoresis (1.5% agarose), and the 538 nucleotide fragment was quantified by band scanning (HP Jet Imager). The amount of HBV recovered from untreated cells is assumed to be 100%. Data from the 6-day time point are presented in Figure 1 as the average values from at least three separate flasks, and the standard error was never greater than 20%, with an average error of 12%.

For each of the three time point series tested, the combination of 3TC plus N-nonyl-DNJ was significantly more effective in inhibiting HBV secretion than either compound alone. Conclusions based upon PCR analysis alone make it difficult to assign precise IC-50 values. The extreme sensitivity and delicate nature of PCR, for example, may account for the inability to achieve greater than 90%

inhibition of HBV by 3TC alone, even at 300nM. Every experiment included controls to assure that PCR was performed in a range of concentrations of DNA in which the reaction yields results proportional to the amount of DNA in the sample. Resolution is approximately 3-fold, i.e., 3-fold differences in DNA concentrations can be detected. The inability to consistently detect less than 3-fold differences probably explains the failure of 3TC alone to achieve 90% inhibition. This suggests that a very high standard of inhibition must be met for the PCR to detect inhibition. Consequently, the trend, over three separate time points, is clear: the combined effect of 3TC plus N-nonyl-DNJ is greater than that of either compound alone, or the additive individual effects of each compound. These data suggest that the IC-50 of 3TC has been moved from about 60 nM to about 0.48 nM when 0.016 g/ml N-nonyl-DNJ is present.

#### Example 5

##### Anti-Hepatitis B Virus Effect of N-nonyl-DNJ Alone in a Woodchuck Model

In order to evaluate the efficacy of N-nonyl-DNJ in combination with 3TC (or other nucleoside or nucleotide analogs) against Hepatitis B virus in a woodchuck animal model, an monotherapy experiment using N-nonyl-DNJ alone was first conducted. This was necessary to determine if N-nonyl-DNJ has any anti-HBV effect in the woodchuck and, if N-nonyl-DNJ has a beneficial effect, to design a combination study based on the dose-response relationship of this drug alone.

Therefore, five groups of four animals each (all groups had both sexes, all but the control had two of each sex) were assigned to 0, 12.5, 25, 50, and 100 mg/kg/day with BID oral dosing. These were lab-reared wild animals. All animals were infected with woodchuck hepatitis virus (WHV) as neonates, and had been tested positive on serological

tests for WHV surface antigen. Blood samples were drawn one week prior to dosing (-1 week), immediately before dosing (0 weeks), weekly during dosing (1, 2, 3, and 4 weeks), and after the end of dosing (5, 6, 8, and 10 weeks).

5        There are two measures of drug efficacy: reduction in total HBV DNA (measured by quantitative PCR), and reduction in HBV DNA from capsids with intact surface glycoproteins, which is the active form of the virus (measured by an ELISA-like immune precipitation assay followed by quantitative  
10        PCR). Cell culture experiments with N-nonyl-DNJ demonstrated little or no effect of this compound on total HBV DNA, but a marked effect on the immune precipitated DNA (IPDNA). Not surprisingly, the IPDNA assay is quite  
15        variable; as a partial compensation for this, four assay runs were conducted, each containing samples from all animals, but different subsets of the study weeks.

      To summarize the results, N-nonyl-DNJ had no effect on total HBV DNA measurements, which were essentially constant for all dose levels over the pre-dose and dosed portions of  
20        the study. On the other hand, IPDNA levels were not constant over the study period. The low dose animals tended to have increasing levels of IPDNA over the dosing period (weeks 0-4), while high dose animals tended to have decreasing levels of IPDNA over the same period. Fitting a  
25        straight line to each animal's weekly responses gave a significant difference in the slope of these lines due to either dose or plasma level of drug. The plasma levels of drug were also quite variable: animals with the lowest plasma levels in their dose group had lower plasma levels  
30        than the animals with the highest plasma levels from the next lower dose group. There were no differences between responses of males and females on any of the measures.

#### Plasma Levels

      There were no clear patterns in the changes in plasma  
35        levels of N-nonyl-DNJ which could be related to week of

dosing or time since previous dose. Because the plasma levels within an animal seemed reasonably consistent during dosing, the median plasma level for each animal was used for subsequent modeling. The plasma levels for each week of the dosing period are plotted for each animal vs. dose (a small amount of random noise is added to the dose level so points which would lie on top of each other on the plot can be distinguished) (Figure 2).

#### HBV DNA

The total HBV DNA levels were essentially constant over time within each animal (data not shown). There was a faint hint of a dose-response relationship with decreasing levels of virus with increasing levels of drug, except that three animals at the highest dose had very high virus levels. It is not possible to conclude that there is any relationship between dose of N-nonyl-DNJ and total HBV DNA. It is possible that there are two populations of animals, responders (such as animal r) and non-responders (animals i, m, and d), but more data would be required to permit a firm conclusion on this point.

#### Immune Precipitated HBV DNA

Substantial variation existed in the IPDNA assay, both between assay runs and within assay runs (data not shown). Even so, it was possible to observe and model a slope over weeks 0-4 which is generally increasing for low dose animals and decreasing for high dose animals. This change in slope was statistically significant ( $p < 0.005$ ).

Before models are fitted to the data, a log transform was applied because: 1) the variation in IPDNA increases with increasing IPDNA values; the log transformation gives values with a nearly constant variation, and 2) it is expected that drug effects will appear as a constant multiplier of the IPDNA level. Because there are zero values of IPDNA, a small value (about 1/2 of the smallest

non-zero value) was added to all values before the log transform.

Two approaches were used to model the changes in slope to week with dose of N-nonyl-DNJ: a linear modeling approach and a nonlinear model. Both approaches assume that the (linear) rate of change of the Log(IPDNA) measure over the dosing period is the "right" measure to reflect the effect of the drug on the virus. Both approaches are fit in stages, and the first stage is common to both approaches. First, a simple straight line regression model is fit using weeks 0-4 to predict  $\log(\text{IPDNA}_{+10})$  separately for each animal by run combination. In the second stage, the response variable is the slope fitted in the first stage.

For the linear approach, a model is fit with slope to week as the response where run is considered a block, dose has a significant effect (almost all of this effect is due to a slope to dose), and the relevant error for testing the effect of dose is the variation among animals treated alike (after the adjustment for the runs as blocks). This is similar to using the calibration data within each run to first adjust each run's data to a common virus DNA concentration; the difference is that here the data from the woodchucks are used for the run adjustment rather than only the calibration data.

For the nonlinear approach, a four parameter logistic model is fit with the slope to week as the response and the dose as the predictor. Again, run is considered a block, but because no run has all weeks, it is not possible to fully reflect the blocking in the nonlinear approach. Even so, the nonlinear model yields an EC50 of 7.88 mg/kg/BID dose. The average maximum slope observed was 2.71 additional  $\log(\text{IPDNA g/mL})/\text{week}$ , or an increase of about 150%/week, the average minimum slope observed with N-nonyl-DNJ is 0.31 fewer  $\log(\text{IPDNA g/mL})/\text{week}$ , or about a decrease of about 25%/week. The slopes, the fitted model, the parameter estimates from the model, and the approximate



standard errors for these parameters are all shown in Figure 3. The data indicate an approximate effective monotherapy dose of N-nonyl-DNJ in woodchucks of about 16 mg/kg/day. Whether in woodchucks or humans, the effective dose of both the N-alkyl-DNJ and nucleoside or nucleotide antiviral agent administered in combination therewith can be administered in two equal daily subdoses (i.e., B.I.D.).

Figures 2 and 3 show letters to indicate animals. Table 4 shows two of the animal codes, the sex, and the dose.

TABLE 4

## Animal Codes, Sex, and Dose

	Animal Number	Letter Code	Sex	Dose
	F95343	b	F	0
5	M96364	n	M	0
	F96304	k	F	0
	F96301	j	F	0
	M96285	h	M	6.25
	F96283	g	F	6.25
10	F96391	o	F	6.25
	M96305	l	M	6.25
	F96271	f	F	12.5
	M96256	e	M	12.5
	M96404	s	M	12.5
15	F96392	p	F	12.5
	F96163	c	F	25
	M96414	t	M	25
	F96393	q	F	25
	M95322	a	M	25
20	M96286	i	M	50
	F96231	d	F	50
	F96402	r	F	50
	M96363	m	M	50

## Example 6

25                   Antiviral Study to Test the Activity of  
                       N-nonyl-DNJ in Combination with 3TC

in a Woodchuck Model of Hepatitis B Virus Infection

The combined activity of N-nonyl-DNJ and the nucleoside analog 3TC can be assessed using the woodchuck model of

30   hepatitis B virus infection. Twenty-eight woodchucks with persistent woodchuck hepatitis virus (WHV) infection can be utilized. Groups of woodchucks can be treated orally with 3TC alone (s.i.d.), with N-nonyl-DNJ alone (b.i.d.), or with combinations of the two drugs. The antiviral activity of

the individual drugs and combinations can be assessed by measuring serum WHV DNA during treatment, and comparing the results of treated groups to placebo treated controls.

Twenty-eight woodchucks with established persistent WHV infection can be used, all of which were experimentally infected with WHV during the first week of life. All can be WHsAg positive at the time the study is initiated.

A total of eight experimental groups can be used. Woodchucks in each group can be stratified on the basis of gender, body weight, and age. 3TC can be administered orally as an aqueous suspension of Epivir (Glaxo-Wellcome) tablets one time per day. N-nonyl DNJ can also be administered orally in aqueous solution, in two divided doses. Treatment with both drugs can be followed by the administration of 4 to 5 mls of semisynthetic liquid woodchuck diet to insure complete ingestion of the drugs.

The experimental groups can be as follows:

	Group	No.	3TC	N-nonly-DNJ
	ID	(mg/kg/day)	(mg/kg/day)	
20	1	4	0.0	0.0
	2	3	3.0	0.0
	3	3	9.0	0.0
	4	3	0.0	4.0
25	5	3	0.0	12.0
	6	4	1.5	2.0
	7	4	4.5	6.0
	8	4	9.0	12.0

Woodchucks can be anesthetized (50mg/kg ketamine, 5mg/kg zylazine), weighed, and blood samples obtained prior to initial treatment, at weekly intervals during the six week period of treatment, and at 1, 2, and 4 weeks following treatment. Serum can be harvested and divided into aliquots. One aliquot can be used for analysis of WHV DNA

by dot blot hybridization and for WHsAg by ELISA. CBCs and clinical biochemical profiles can be obtained prior to treatment and at the end of treatment. A second aliquot can be maintained as an archive sample. Other aliquots of serum  
5 can be used for drug analysis and special WHV DNA analyses.

#### Example 7

#### Anti-Hepatitis B Virus Activity of N-Substituted-1,5-Dideoxy-1,5-Imino-D-Glucitol Compounds *In Vitro*

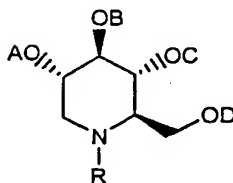
10 The anti-hepatitis B virus activity and effect on cell viability of a number of different N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds is assessed using an *in vitro* assay employing chronically hepatitis B virus secreting HepG2.2.15 cells. The method employed is  
15 essentially that described in Block et al. (1994) Proc. Natl. Acad. Sci. USA 91:2235-2239. The compounds are of Formula I where R is: 4-(4-trifluoromethylphenyl)-butyl, 4-(4-trifluoromethylphenyl)-butane-1-carbonyl,  
4-(4-trifluoromethoxyphenyl)-butyl, 4-(4-trifluoromethoxyphenyl)-butane-1-carbonyl,  
20 2-cyclohexylethyl, 2-(4-thiapyran)-ethyl, 5-(morpholinyl)-pentyl, 4-(4-pyridineoxy)-butyl, 3-(3-pyridyl)-propyl, 4-(4-trifluoromethylthiaphenyl)-butyl, 7-(trifluoromethylsulfonyl)-heptyl, 4-(4-trifluoromethylthia-  
25 phenyl)-butyl, 8-(trifluoromethylsulfonylamino)-octyl, 12,12,12-trifluoro-6,8-dioxa-dodecyl, 10,10,10-trifluoro-5-oxa-decyl, 12,12,12,11,11-pentafluoro-6-oxa-dodecyl, 9,9,9-trifluoro-2-oxa-nonyl, 5-(4-trifluoromethylphenyl)-4-oxa-butyl, 4-(4-trifluoromethylphenyl)-3-oxa-propyl, 4-(4-  
30 trifluoromethylphenyl)-3-oxa-propanoyl, 5-cyclohexyl-4-oxabutyl, 5-(4-trifluoromethoxyphenyl)-4-oxa-butyl and 5-(4-trifluoromethylthiaphenyl)-4-oxa-butyl.

The invention being thus described, it will be obvious that the same can be varied in many ways. Such variations  
35 are not to be regarded as a departure from the spirit and

scope of the present invention, and all such modifications and equivalents as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

What Is Claimed Is:

1. A method for treating a hepatitis virus infection in a mammal, comprising administering to said mammal an anti-hepatitis virus effective amount of at least one N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

- 10 R is alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, cycloalkenylalkyl, cycloalkenylalkenyl, cycloalkenylalkynyl, bicycloalkenylalkyl, tricycloalkenylalkyl, tetracycloalkenylalkyl, bicycloalkenoxyalkyl, tricycloalkenoxyalkyl, tetracycloalkenyloxyalkyl,
- 15 cycloalkylalkenyl, cycloalkylalkynyl, aralkenyl, aralkynyl, substituted aralkyl, aralkoxyalkyl, aralkoxyalkenyl, aralkoxyalkynyl, aralkenoxyalkyl, aralkenoxyalkenyl, heteroarylalkyl, heterocyclooxyalkyl, heterocyclothiaalkyl, heterocycloalkenyl, heteroarylakenyl, heteroarylalkynyl,
- 20 aryloxyalkyl, aryloxyalkenyl, aryloxyalkynyl, haloalkyl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkenyl, dihydroxyalkenyl, hydroxyalkynyl, haloalkyloxyalkyl,

haloalkoxyalkenyl, haloalkoxyalkynyl, carbonyl,  
cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkylcarbonyl,  
25 alkenylcarbonyl, alkynylcarbonyl, arylcarbonylalkyl,  
arylalkylcarbonyl, arylalkenylcarbonyl,  
arylalkyloxyalkyl, aryloxyalkylcarbonyl,  
aryloxyalkylcarbonyl, haloalkylcarbonyl,  
hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl,  
30 cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl,  
alkyloxyalkylcarbonyl, alkanoyloxyalkyl, aryloxyalkoxyalkyl,  
aryloxyalkyl, aminoalkyl, amino(alkyl), alkanoylaminoalkyl,  
aminocarbonylalkyl, hydroxysulfonealkyl, aminosulfonealkyl,  
aminocarbonylaminoalkyl, aroylaminoalkyl,  
35 alkoxy-carbonylaminoalkyl, carboxyalkyl, alkoxy-carbonylalkyl,  
perhaloalkylaralkyl, or  $R^5$ , wherein

$$R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_p \quad R^6 - \text{wherein:}$$

$R^1$  is alkyl, aryl, alkenyl, alkynyl, hydrogen or  
haloalkyl;

40  $R^2$  is independently alkylene, alkenylene, alkynylene or  
haloalkylene;

$R^3$  is independently alkylene, alkenylene, alkynylene or  
haloalkylene;

$R^4$  is independently alkylene, alkenylene, alkynylene or  
45 haloalkylene;

$R^6$  is independently alkylene, alkenylene, alkynylene or  
haloalkylene;

$X^1$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

50  $X^2$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

$X^3$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

$X^4$  is independently oxygen, sulfur, sulfoxide or  
55 sulfone;

m, n and p are independently 0, 1, 2, or 3; and

$m + n + p \leq 3$

A, B, C, and D are independently hydrido, lower alkyl, lowerhaloalkyl or acyl;

60 D and R taken together may form a five or six membered ring when R is carbonyl or alkylcarbonyl;

A and B taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

B and C taken together with the atoms to which they are  
65 attached may form a five or six membered heterocyclic ring;  
and

C and D taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

70 wherein the main chain in R contains between one and twenty atoms; and

the main chain of  $R^5$  containing between four and twenty atoms.

2. A process as set forth in claim 1 wherein said the aryl, heteroaryl, or heterocyclo moiety of a substituent comprising R is substituted with a substituent selected from the group consisting of carboxy, amino, nitro, hydroxy,  
5 halo, alkylcarbonyl, alkanoyloxy, sulfo, alkoxy, alkylthio, methylenedioxy, alkyl, alkanoylamino, alkylamino, aryl, heterocycloalkyl, silyl and substituted silyl.

3. The method of claim 1, wherein said pharmaceutically acceptable salt is selected from the group consisting of acetate, adipate, alginate, citrate, phosphate, aspartate, benzoate, benzenesulfonate, bisulfate,  
5 butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate,



hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, 10 oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate, and undecanoate.

4. A method as set forth in claim 1 wherein R is selected from the group consisting of aryloxyalkyl, monohaloalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkenylcarbonyl, alkynylcarbonyl, 5 arylalkylcarbonyl, arylalkyloxycarbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, perhaloalkylaralkyl, or R<sup>5</sup>.

5. A method as set forth in claim 4 wherein when all of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> linkages are oxygen: (m + n + p) ≥ 2; and R<sup>1</sup> is not hydrogen or unsubstituted alkyl, or not all of any R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> groups are unsubstituted alkylene.

6. A method as set forth in claim 4 wherein R is R<sup>5</sup>.

7. A method as set forth in claim 1 wherein R is alkenyl, alkynyl, substituted arylalkyl, aryloxyalkyl, haloalkyl, hydroxyalkyl, haloalkyloxyalkyl, carbonyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkylcarbonyl, 5 alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, arylalkyloxycarbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl,

haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, alkyloxycarbonyl or R<sup>5</sup>.

8. A method as set forth in claim 7 wherein R is R<sup>5</sup>.

9. A method as set forth in claim 1 wherein each of A, B, C and D is hydrido.

10. A method as set forth in claim 1 wherein each of A, B, C and D is lower alkyl, lower haloalkyl or acyl.

11. A method as set forth in claim 1 wherein R is aryloxyalkoxyalkyl, alkylcarbonyloxyalkyl, alkyl, arylcarbonyloxyalkyl, aminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, aminocarbonylaminoalkyl, aminothiocabonylaminoalkyl, alkenyl, arylalkenyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, aminothiocabonylalkyl, aminosulfonealkyl, arylalkynyl, heterocycloalkyl, heteroarylalkyl, heteroaryloxyalkyl, heteroarylthiaalkyl, heterocyclooxyalkyl, heterocyclothiaalkyl, aryloxyalkyl, arylthiaalkyl, monohaloalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, perhaloalkylaralkyl, and R<sup>5</sup>.

12. A method as set forth in claim 11 wherein when all of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> are oxygen: (m + n + p) ≥ 2; and R<sup>1</sup> is not hydrogen or unsubstituted alkyl, or not all of any R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> groups unsubstituted alkylene.

13. A method as set forth in claim 1 wherein R is carbonyl, alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, aryloxyalkyl, aryloxyalkylcarbonyl,

- haloalkylcarbonyl, hydroxyalkylcarbonyl,  
5 haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl,  
alkoxyalkylcarbonyl, cycloalkylalkylcarbonyl,  
alkoxycarbonyl, alkylcarbonyl, aryloxyalkoxyalkylcarbonyl,  
alkylcarbonyloxyalkylcarbonyl, arylcarbonyloxyalkylcarbonyl,  
aminoalkylcarbonyl, alkylcarbonylaminoalkylcarbonyl,  
10 arylcarbonylaminoalkylcarbonyl,  
alkoxycarbonylaminoalkylcarbonyl,  
aminocarbonylaminoalkylcarbonyl,  
aminothiocabonylaminoalkylcarbonyl, arylalkenylcarbonyl,  
carboxyalkylcarbonyl, alkoxycarbonylalkylcarbonyl,  
15 aminocarbonylalkylcarbonyl, aminothiocabonylalkylcarbonyl,  
aminosulfonealkylcarbonyl, arylalkynylcarbonyl,  
heterocycloalkylcarbonyl, heteroarylalkyl,  
heteroaryloxyalkyl, heteroarylthiaalkylcarbonyl,  
heterocyclooxyalkylcarbonyl, heterocyclothiaalkylcarbonyl,  
20 arylthiaalkylcarbonyl, monohaloalkylcarbonyl,  
haloalkyloxyalkylcarbonyl, cycloalkylalkyloxyalkylcarbonyl  
and R<sup>5</sup>.

14. A method as set forth in claim 13 when all of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> are oxygen:  $(m + n + p) \geq 2$ ; and R<sup>1</sup> is not hydrogen or unsubstituted alkyl, or not all of any R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> groups unsubstituted alkylene.

15. A method as set forth in claim 1 wherein R is R<sup>5</sup>, A and B are hydrido, and C and D taken together with the atoms to which they are attached may form a five or six membered ring.

16. A method as set forth in claim 1 wherein R is selected from the group consisting of: aryloxyalkyl,

monoalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl and R<sup>5</sup>.

17. A method as set forth in claim 1 wherein R is selected from the group consisting of alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, arylalkyloxy carbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, and alkoxyalkylcarbonyl.

18. A method as set forth in claim 1 wherein the compound of Formula I that is administered to said mammal is produced from an intermediate also corresponding to Formula I, wherein R in said intermediate is alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, aryloxyalkyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, cycloalkylalkylcarbonyl, alkoxycarbonyl, alkylcarbonyl, aryloxyalkoxyalkylcarbonyl, alkylcarbonyloxyalkylcarbonyl, arylcarbonyloxyalkylcarbonyl, aminoalkylcarbonyl, alkylcarbonylaminoalkylcarbonyl, arylcarbonylaminoalkylcarbonyl, alkoxycarbonylaminoalkylcarbonyl, aminocarbonylaminoalkylcarbonyl, aminothiocarbonylaminoalkylcarbonyl, arylalkenylcarbonyl, carboxyalkylcarbonyl, alkoxycarbonylalkylcarbonyl, aminocarbonylalkylcarbonyl, aminothiocarbonylalkylcarbonyl, aminosulfonealkylcarbonyl, arylalkynylcarbonyl, heterocycloalkylcarbonyl, heteroarylalkylcarbonyl, heteroaryloxyalkylcarbonyl, heteroarylthiaalkylcarbonyl, heterocyclooxyalkylcarbonyl, heterocyclothiaalkylcarbonyl, arylthiaalkylcarbonyl, monohaloalkylcarbonyl,

haloalkyloxyalkylcarbonyl, cycloalkylalkyloxyalkylcarbonyl,  
25 or R<sup>5</sup>carbonyl.

19. A method as set forth in claim 1 wherein the compound of Formula I that is administered to said mammal is produced from an intermediate also corresponding to Formula I, wherein R in said intermediate is aryloxyalkylcarbonyl,  
5 haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, cycloalkylalkylcarbonyl, aryloxyalkoxyalkylcarbonyl, arylcarbonyloxyalkylcarbonyl, aminoalkylcarbonyl, alkylcarbonylaminoalkylcarbonyl,  
10 arylcarbonylaminoalkylcarbonyl, alkoxycarbonylaminoalkylcarbonyl, aminocarbonylaminoalkylcarbonyl, aminothiocabonylaminoalkylcarbonyl, carboxyalkylcarbonyl, alkoxycarbonylalkylcarbonyl, aminocarbonylalkylcarbonyl,  
15 aminothiocabonylalkylcarbonyl, aminosulfonealkylcarbonyl, arylalkynylcarbonyl, heterocycloalkylcarbonyl, heteroarylalkylcarbonyl, heteroaryloxyalkylcarbonyl, heteroarylthiaalkylcarbonyl, heterocyclooxyalkylcarbonyl, heterocyclothiaalkylcarbonyl, arylthiaalkylcarbonyl,  
20 monohaloalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkylalkyloxyalkylcarbonyl, or R<sup>5</sup>carbonyl.

20. A method as set forth in claim 1 wherein the compound of Formula I that is administered to said mammal is produced from an intermediate also corresponding to Formula I, wherein R in said intermediate is R<sup>5</sup>carbonyl.

21. A method as set forth in claim 1 wherein the compound of Formula I that is administered to said mammal is produced from an intermediate also corresponding to Formula

I, wherein R in said intermediate is aryloxyalkylcarbonyl,  
5 haloalkylcarbonyl, hydroxyalkylcarbonyl,  
haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl,  
alkoxyalkylcarbonyl, cycloalkylalkylcarbonyl,  
aryloxyalkoxyalkylcarbonyl, arylcarbonyloxyalkylcarbonyl,  
aminoalkylcarbonyl, alkylcarbonylaminoalkylcarbonyl,  
10 arylcarbonylaminoalkylcarbonyl,  
alkoxycarbonylaminoalkylcarbonyl,  
aminocarbonylaminoalkylcarbonyl,  
aminothiocarbonylaminoalkylcarbonyl, carboxyalkylcarbonyl,  
alkoxycarbonylalkylcarbonyl, aminocarbonylalkylcarbonyl,  
15 aminothiocarbonylalkylcarbonyl, aminosulfonealkylcarbonyl,  
arylalkynylcarbonyl, heterocycloalkylcarbonyl,  
heteroarylalkylcarbonyl, heteroaryloxyalkylcarbonyl,  
heteroarylthiaalkylcarbonyl, heterocyclooxyalkylcarbonyl,  
heterocyclothiaalkylcarbonyl, arylthiaalkylcarbonyl,  
20 monohaloalkylcarbonyl, haloalkyloxyalkylcarbonyl, or  
cycloalkylalkyloxyalkylcarbonyl.

22. A method as set forth in claim 1 wherein R is  
aryloxyalkoxyalkyl, alkyl, aminoalkyl,  
arylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl,  
aminocarbonylaminoalkyl, alkenyl, arylalkenyl,  
5 aminocarbonylalkyl, aminosulfonealkyl, arylalkynyl,  
heterocycloalkyl, heteroarylalkyl, heteroaryloxyalkyl,  
heteroarylthiaalkyl, heterocyclooxyalkyl,  
heterocyclothiaalkyl, aryloxyalkyl, arylthiaalkyl,  
monohaloalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl,  
10 cycloalkylalkyloxyalkyl, perhaloalkylaralkyl, or R<sup>5</sup>.

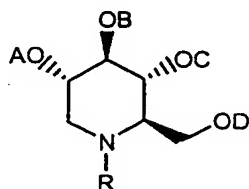
23. A method as set forth in claim 22 wherein:  
(m+n+p)≥2; and R<sup>1</sup> is not hydrogen or unsubstituted alkyl, or

not all of  $R^2$ ,  $R^3$ , and  $R^4$  are unsubstituted alkylene; when all of  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  are oxygen.

24. A method as set forth in claim 1 wherein R is aryloxyalkoxyalkyl, alkyl, aminoalkyl, arylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, aminocarbonylaminoalkyl, alkenyl, arylalkenyl, 5 aminocarbonylalkyl, aminosulfonealkyl, arylalkynyl, heterocycloalkyl, heteroarylalkyl, heteroaryloxyalkyl, heteroarylthiaalkyl, heterocyclooxyalkyl, heterocyclothiaalkyl, aryloxyalkyl, arylthiaalkyl, monohaloalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, 10 cycloalkylalkyloxyalkyl or perhaloalkylaralkyl.

25. A method as set forth in claim 24 wherein R is trifluoromethylaralkyl.

26. A method for treating a hepatitis virus infection in a mammal, comprising administering to said mammal an anti-hepatitis virus effective amount of an antiviral composition comprising at least one 5 N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof



Formula I

wherein:

R is alkenyl, alkynyl, cycloalkyl, aryl,  
 10 cycloalkenylalkyl, bicycloalkenylalkyl,  
 tricycloalkenylalkyl, tetracycloalkenyloxyalkyl, aralkenyl,  
 aralkynyl, substituted aralkyl, heteroarylalkyl,  
 heterocyclooxyalkyl, heterocyclothiaalkyl,  
 heterocycloalkenyl, heteroarylakenyl, heteroarylalkynyl,  
 15 aryloxyalkyl, haloalkyl, hydroxyalkyl, haloalkyloxyalkyl,  
 carbonyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl,  
 alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl,  
 arylcarbonylalkyl, arylalkylcarbonyl, arylalkyloxycarbonyl,  
 aryloxyalkylcarbonyl, haloalkylcarbonyl,  
 20 hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl,  
 cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl,  
 alkylloxycarbonyl, alkanoyloxyalkyl, aryloxyalkoxyalkyl,  
 aroyloxyalkyl, aminoalkyl, alkanoylaminoalkyl,  
 alkanoylalkyl, aminocarbonylalkyl, hydroxysulfonealkyl,  
 25 aminosulfonealkyl, aminocarbonylaminoalkyl,  
 aroylaminoalkyl, alkoxycarbonylaminoalkyl, carboxyalkyl,  
 alkoxycarbonylalkyl, perhaloalkylaralkyl or  $R^5$ , wherein

$R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_pR^6-$ , wherein:

$R^1$  is alkyl, aryl, alkenyl, alkynyl, hydrogen or  
 30 haloalkyl;  
 $R^2$  is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;  
 $R^3$  is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;  
 35  $R^4$  is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;  
 $R^6$  is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;  
 $X^1$  is independently oxygen, sulfur, sulfoxide or  
 40 sulfone;



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$X^2$  is independently oxygen, sulfur, sulfoxide or sulfone;

$X^3$  is independently oxygen, sulfur, sulfoxide or sulfone;

45  $X^4$  is independently oxygen, sulfur, sulfoxide or sulfone;

$m$ ,  $n$  and  $p$  are independently 0, 1, 2, or 3; and

$m + n + p \leq 3$

A, B, C, and D are independently hydrido, lower alkyl, 50 lowerhaloalkyl or acyl;

D and R taken together may form a five or six membered ring when R is carbonyl or alkylcarbonyl;

A and B taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

55 B and C taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

C and D taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

wherein the main chain in R contains between one and 60 twenty atoms; and

the main chain of  $R^5$  containing between four and twenty atoms.

27. A method as set forth in claim 26 wherein R is selected from the group consisting of aryloxyalkyl, monohaloalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkenylcarbonyl, alkynylcarbonyl, 5 arylalkylcarbonyl, arylalkyloxycarbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, perhaloalkylaralkyl or  $R^5$ .

28. A method as set forth in claim 27 wherein all of any  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  linkages are oxygen:  $(m + n + p) \geq 2$ ; and  $R^1$  is not hydrogen or unsubstituted alkyl, or not all of any  $R^2$ ,  $R^3$ , and  $R^4$  groups are unsubstituted alkylene.

29. A method as set forth in claim 28 wherein R is  $R^5$ .

30. A method as set forth in claim 26 wherein R is alkenyl, alkynyl, substituted arylalkyl, aryloxyalkyl, haloalkyl, hydroxyalkyl, haloalkyloxyalkyl, carbonyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, arylalkyloxycarbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, alkyloxycarbonyl, perhaloalkylaralkyl or  $R^5$ .

31. A method as set forth in claim 30 wherein R is  $R^5$ .

32. A method as set forth in claim 26 consisting essentially of administering to said mammal an anti-hepatitis virus effective amount of at least one N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof.

33. A method as set forth in claim 32 wherein R is selected from the group consisting of aryloxyalkyl, hydrohaloalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, arylalkyloxycarbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl,

cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, perhaloalkylaralkyl or R<sup>5</sup>.

34. A method as set forth in claim 33 wherein when all of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> linkages are oxygen: (m + n + p) ≥ 2; and R<sup>1</sup> is not hydrogen or unsubstituted alkyl, or not all of any R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> groups are unsubstituted alkylene.

35. A method as set forth in claim 26 comprising administering to said mammal an anti-hepatitis virus effective amount of an antiviral composition consisting essentially of at least one

5 N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof.

36. A method as set forth in claim 35 wherein R is selected from the group consisting of aryloxyalkyl, monohaloalkyl, haloalkyloxyalkyl, carbonyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, arylalkyloxycarbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, perhaloalkylaralkyl or R<sup>5</sup>.

37. A method as set forth in claim 36 wherein when all of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> linkages are oxygen: (m + n + p) ≥ 2; and R<sup>1</sup> is not hydrogen or unsubstituted alkyl, or not all of any R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> groups are unsubstituted alkylene.

38. A method as set forth in claim 3 consisting essentially of administering to said mammal an anti-hepatitis virus effective amount of an antiviral

composition consisting essentially of at least one  
5 N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of  
Formula I or a pharmaceutically acceptable salt thereof.

39. A method as set forth in claim 38 wherein R is  
selected from the group consisting of aryloxyalkyl,  
haloalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl,  
cycloalkylalkyloxyalkyl, alkenylcarbonyl, alkynylcarbonyl,  
5 arylalkylcarbonyl, arylalkyloxycarbonyl,  
aryloxyalkylcarbonyl, haloalkylcarbonyl,  
hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl,  
cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl,  
perhaloalkylaralkyl or R<sup>5</sup>.

40. A method as set forth in claim 39 when all of any  
X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> linkages are oxygen:  $(m + n + p) \geq 2$ ; and  
R<sup>1</sup> is not hydrogen or unsubstituted alkyl, or not all of any  
R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> groups are unsubstituted alkylene.

41. A method as set forth in claim 26 comprising  
administering to said mammal an anti-hepatitis virus  
effective amount of an antiviral composition containing at  
least one N-substituted-1,5-dideoxy-1,5-imino-D-glucitol  
5 compound of Formula I or a pharmaceutically acceptable salt  
thereof, said administration begin substantially exclusive  
of the administration of any antiviral agent comprising a  
nucleoside, nucleotide, an immunodulator or an  
immunostimulant.

42. A method as set forth in claim 41 wherein R is  
selected from the group consisting of aryloxyalkyl,  
monohaloalkyl, hydroxyalkyl, haloalkyloxyalkyl,  
cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl,

5 alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl,  
arylalkyloxycarbonyl, aryloxyalkylcarbonyl,  
haloalkylcarbonyl, hydroxyalkylcarbonyl,  
haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl,  
alkoxyalkylcarbonyl, alkyloxycarbonyl, perhaloalkylaralkyl  
10 or R<sup>5</sup>.

43. A method as set forth in claim 41 wherein when all of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> linkages are oxygen: (m + n + p) ≥ 2; and R<sup>1</sup> is not hydrogen or unsubstituted alkyl, or not all of any R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> groups are unsubstituted alkylene.

44. A method as set forth in claim 41 wherein said administration is substantially exclusive of the administration of an antiviral agent other than an agent or agent corresponding to Formula 1.

45. A method as set forth in claim 41 comprising treating a hepatitis B virus infection comprising administering to said mammal an anti-hepatitis B virus effective amount of at least one  
5 N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof.

46. A method as set forth in claim 41 comprising treating a hepatitis C virus infection comprising administering to said mammal an anti-hepatitis C virus effective amount of at least one  
5 N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof.

47. A method as set forth in claim 41 consisting essentially of administering to said mammal an

anti-hepatitis virus effective amount of a composition containing an anti-viral agent, said anti-viral agent  
5 consisting essentially of at least one N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof.

48. A method as set forth in claim 47 comprising treating a hepatitis B virus infection comprising administering to said mammal an anti-hepatitis B virus effective amount of at least one  
5 N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof.

49. A method as set forth in claim 47 comprising treating a hepatitis C virus infection comprising administering to said mammal an anti-hepatitis C virus effective amount of at least one  
5 N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof.

50. A method as set forth in claim 47 wherein R is selected from the group consisting of aryloxyalkyl, monohaloalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkylcarbonyl, alkenylcarbonyl,  
5 alkynylcarbonyl, arylalkylcarbonyl, arylalkyloxycarbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, perhaloalkylaralkyl or R<sup>5</sup>.

51. A method as set forth in claim 50 wherein when all of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> linkages are oxygen: (m + n + p) ≥

2; and  $R^1$  is not hydrogen or unsubstituted alkyl, or not all of any  $R^2$ ,  $R^3$ , and  $R^4$  groups are unsubstituted alkylene.

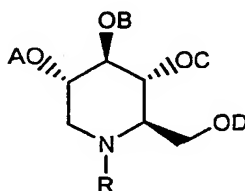
52. A method as set forth in claim 41 comprising treating a hepatitis B virus infection comprising administering to said mammal an anti-hepatitis B virus effective amount of at least one

5 N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof.

53. A method as set forth in claim 41 comprising treating a hepatitis C virus infection comprising administering to said mammal an anti-hepatitis C virus effective amount of at least one

5 N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof.

54. An N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof:



Formula I

5 wherein:

R is aryloxyalkyl, monohaloalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, arylalkyloxycarbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, perhaloalkylaralkyl or  $R^5$ , wherein

$$R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_pR^6-, \text{ wherein}$$

$R^1$  is alkyl, aryl, alkenyl, alkynyl, hydrogen or

15 haloalkyl;

$R^2$  is independently alkylene, alkenylene, alkynylene or haloalkylene;

$R^3$  is independently alkylene, alkenylene, alkynylene or haloalkylene;

20  $R^4$  is independently alkylene, alkenylene, alkynylene or haloalkylene;

$R^6$  is independently alkylene, alkenylene, alkynylene or haloalkylene;

$X^1$  is independently oxygen, sulfur, sulfoxide or  
25 sulfone;

$X^2$  is independently oxygen, sulfur, sulfoxide or sulfone;

$X^3$  is independently oxygen, sulfur, sulfoxide or sulfone;

30  $X^4$  is independently oxygen, sulfur, sulfoxide or sulfone;

$m$ ,  $n$  and  $p$  are independently 0, 1, 2, or 3;

$$(m + n + p) \leq 3;$$

$$(m + n + p) \geq 1;$$

35 when all of any  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  linkages are oxygen;

$(m + n + p) \geq 2$ ; and  $R^1$  is not hydrogen or unsubstituted alkyl; or not all of any  $R^2$ ,  $R^3$  and  $R^4$  groups are unsubstituted alkylene;



A, B, C, and D are independently hydrido, lower alkyl,  
40 lowerhaloalkyl or acyl;

D and R taken together may form a five or six membered  
ring when R is carbonyl or alkylcarbonyl;

A and B taken together with the atoms to which they are  
attached may form a five or six membered heterocyclic ring;

45 B and C taken together with the atoms to which they are  
attached may form a five or six membered heterocyclic ring;

C and D taken together with the atoms to which they are  
attached may form a five or six membered heterocyclic ring;

wherein the main chain in R contains between one and  
50 twenty atoms;

the main chain of  $R^5$  containing between four and twenty  
atoms;

when all of any  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  linkages are oxygen;  
and

55  $(m + n + p) \geq 2$ ; and  $R^1$  is not hydrogen or  
unsubstituted alkyl; or not all of any  $R^2$ ,  $R^3$  and  $R^4$  groups  
are unsubstituted alkylene.

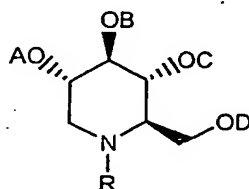
55. A compound as set forth in claim 543 wherein R is  
selected from the group consisting of monohaloalkyl, a  
substituent corresponding to  $R^5$  and haloalkoxyalkyl.

56. A compound as set forth in claim 55 wherein R is  
trifluoroalkoxyalkyl.

57. A compound as set forth in claim 55 wherein R is  
 $R^5$ .

58. A pharmaceutical composition comprising an anti-  
viral compound comprising an N-substituted-1,5-dideoxy-  
1,5-imino-D-glucitol compound or a pharmaceutically

acceptable salt thereof and another antiviral compound  
 5 selected from the group consisting of a nucleoside, a  
 nucleotide, an immunomodulator, an immunostimulant, and  
 mixtures thereof, said N-substituted-1,5-dideoxy-1,5-  
 imino-D-glucitol compound corresponding to Formula I:



Formula I

10 R is alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl,  
 cycloalkenylalkyl, cycloalkenylalkenyl, cycloalkenylalkynyl,  
 bicycloalkenylalkyl, tricycloalkenylalkyl,  
 tetracycloalkenylalkyl, bicycloalkenoxyalkyl,  
 tricycloalkenoxyalkyl, tetracycloalkenyloxyalkyl,  
 15 cycloalkylalkenyl, cycloalkylalkynyl, aralkenyl, aralkynyl,  
 substituted aralkyl, aralkoxyalkyl, aralkoxyalkenyl,  
 aralkoxyalkynyl, aralkenoxyalkyl, aralkenoxyalkenyl,  
 heteroarylalkyl, heterocyclooxyalkyl, heterocyclothiaalkyl,  
 heterocycloalkenyl, heteroarylakenyl, heteroarylalkynyl,  
 20 aryloxyalkyl, aryloxyalkenyl, aryloxyalkynyl, haloalkyl,  
 hydroxyalkyl, dihydroxyalkyl, hydroxyalkenyl,  
 dihydroxyalkenyl, hydroxyalkynyl, haloalkyloxyalkyl,  
 haloalkoxyalkenyl, haloalkoxyalkynyl, carbonyl,  
 cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkylcarbonyl,  
 25 alkenylcarbonyl, alkynylcarbonyl, arylcarbonylalkyl,  
 arylalkylcarbonyl, arylalkenylcarbonyl,

- arylalkyloxycarbonyl, aryloxyalkylcarbonyl,  
haloalkylcarbonyl, hydroxyalkylcarbonyl,  
haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl,  
30 alkoxyalkylcarbonyl, alkyloxycarbonyl, alkanoyloxyalkyl,  
aryloxyalkoxyalkyl, aroyloxyalkyl, aminoalkyl, amino(alkyl),  
alkanoylaminoalkyl, aminocarbonylalkyl, hydroxysulfonealkyl,  
aminosulfonealkyl, aminocarbonylaminoalkyl,  
aroylaminoalkyl, alkoxycarbonylaminoalkyl, carboxyalkyl,  
35 alkoxycarbonylalkyl, perhaloalkylaralkyl, or  $R^5$ , wherein  
 $R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_pR^6-$ , wherein:  
 $R^1$  is alkyl, aryl, alkenyl, alkynyl, hydrogen or  
haloalkyl;  
 $R^2$  is independently alkylene, alkenylene, alkynylene or  
40 haloalkylene;  
 $R^3$  is independently alkylene, alkenylene, alkynylene or  
haloalkylene;  
 $R^4$  is independently alkylene, alkenylene, alkynylene or  
haloalkylene;  
45  $R^6$  is independently alkylene, alkenylene, alkynylene or  
haloalkylene;  
 $X^1$  is independently oxygen, sulfur, sulfoxide or  
sulfone;  
 $X^2$  is independently oxygen, sulfur, sulfoxide or  
50 sulfone;  
 $X^3$  is independently oxygen, sulfur, sulfoxide or  
sulfone;  
 $X^4$  is independently oxygen, sulfur, sulfoxide or  
sulfone;  
55  $m$ ,  $n$  and  $p$  are independently 0, 1, 2, or 3; and  
 $m + n + p \leq 3$   
 $A$ ,  $B$ ,  $C$ , and  $D$  are independently hydrido, lower alkyl,  
lowerhaloalkyl or acyl;

D and R taken together may form a five or six membered  
60 ring when R is carbonyl or alkylcarbonyl;

A and B taken together with the atoms to which they are  
attached may form a five or six membered heterocyclic ring;

B and C taken together with the atoms to which they are  
attached may form a five or six membered heterocyclic ring;  
65 and

C and D taken together with the atoms to which they are  
attached may form a five or six membered heterocyclic ring;

wherein the main chain in R contains between one and  
twenty atoms; and

70 the main chain of R<sup>5</sup> containing between four and twenty  
atoms.

59. A composition as set forth in claim 58 comprising  
a first amount of said compound of Formula I and a second  
amount of an antiviral compound selected from the group  
consisting of a nucleoside antiviral compound, a nucleotide  
5 antiviral compound, an immunomodulator, an immunostimulant,  
and mixtures thereof,

wherein said first and second amounts of said compounds  
together comprise an anti-hepatitis virus effective amount  
of said compounds.

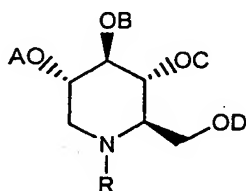
60. A composition as set forth in claim 58 further  
comprising a pharmaceutically acceptable, carrier, diluent  
or excipient.

61. A pharmaceutical composition as set forth in claim  
58 wherein R is selected from the group consisting of  
aryloxyalkyl, monohaloalkyl, haloalkyloxyalkyl,  
cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl,  
5 alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl,

arylalkyloxycarbonyl, aryloxyalkylcarbonyl,  
haloalkylcarbonyl, hydroxyalkylcarbonyl,  
haloalkyloxylalkylcarbonyl, cycloalkyloxylalkylcarbonyl,  
alkoxyalkylcarbonyl, perhaloalkylaralkyl or R<sup>5</sup>.

62. A pharmaceutical composition as set forth in claim  
61 wherein when all of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> linkages are  
oxygen: (m + n + p) ≥ 2; and R<sup>1</sup> is not hydrogen or  
unsubstituted alkyl, or not all of any R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> groups  
5 are unsubstituted alkylene.

63. A salt of an N-substituted-1,5-dideoxy-  
1,5-imino-D-glucitol compound and an antiviral compound  
selected from the group consisting of a nucleoside having an  
acid moiety and a nucleotide, said N-substituted-1,5-  
5 dideoxy-1,5-imino-D-glucitol compound corresponding to  
Formula I:



Formula I

wherein:

R is alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl,  
10 cycloalkenylalkyl, cycloalkenylalkenyl, cycloalkenylalkynyl,  
bicycloalkenylalkyl, tricycloalkenylalkyl,

tetracycloalkenylalkyl, bicycloalkenoxyalkyl,  
 tricycloalkenoxyalkyl, tetracycloalkenyloxyalkyl,  
 cycloalkylalkenyl, cycloalkylalkynyl, aralkenyl, aralkynyl,  
 15 substituted aralkyl, aralkoxyalkyl, aralkoxyalkenyl,  
 aralkoxyalkynyl, aralkenoxyalkyl, aralkenoxyalkenyl,  
 heteroarylalkyl, heterocyclooxyalkyl, heterocyclothiaalkyl,  
 heterocycloalkenyl, heteroarylakenyl, heteroarylalkynyl,  
 aryloxyalkyl, aryloxyalkenyl, aryloxyalkynyl, haloalkyl,  
 20 hydroxyalkyl, dihydroxyalkyl, hydroxyalkenyl,  
 dihydroxyalkenyl, hydroxyalkynyl, haloalkyloxyalkyl,  
 haloalkoxyalkenyl, haloalkoxyalkynyl, carbonyl,  
 cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkylcarbonyl,  
 alkenylcarbonyl, alkynylcarbonyl, arylcarbonylalkyl,  
 25 arylalkylcarbonyl, arylalkenylcarbonyl,  
 arylalkyloxycarbonyl, aryloxyalkylcarbonyl,  
 haloalkylcarbonyl, hydroxyalkylcarbonyl,  
 haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl,  
 alkoxyalkylcarbonyl, alkyloxycarbonyl, alkanoyloxyalkyl,  
 30 aryloxyalkoxyalkyl, aroyloxyalkyl, aminoalkyl,  
 alkanoylaminoalkyl, aminocarbonylalkyl, hydroxysulfonealkyl,  
 aminosulfonealkyl, aminocarbonylaminoalkyl,  
 aroylaminoalkyl, alkoxycarbonylaminoalkyl, carboxyalkyl,  
 alkoxycarbonylalkyl, perhaloalkylaralkyl or R<sup>5</sup>, wherein

35  $R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_pR^6-$ , wherein:

R<sup>1</sup> is alkyl, aryl, alkenyl, alkynyl, hydrogen or  
 haloalkyl;

R<sup>2</sup> is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;

40 R<sup>3</sup> is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;

R<sup>4</sup> is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;

$R^6$  is independently alkylene, alkenylene, alkynylene,  
45 or haloalkylene;

$X^1$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

$X^2$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

50  $X^3$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

$X^4$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

$m$ ,  $n$  and  $p$  are independently 0, 1, 2, or 3; and  
55  $m + n + p \leq 3$

$A$ ,  $B$ ,  $C$ , and  $D$  are independently hydrido, lower alkyl,  
lowerhaloalkyl or acyl;

$D$  and  $R$  taken together may form a five or six membered  
ring when  $R$  is carbonyl or alkylcarbonyl;

60  $A$  and  $B$  taken together with the atoms to which they are  
attached may form a five or six membered heterocyclic ring;

$B$  and  $C$  taken together with the atoms to which they are  
attached may form a five or six membered heterocyclic ring;  
and

65  $C$  and  $D$  taken together with the atoms to which they are  
attached may form a five or six membered heterocyclic ring;

wherein the main chain in  $R$  contains between one and  
twenty atoms; and

the main chain of  $R^5$  containing between four and twenty  
70 atoms.

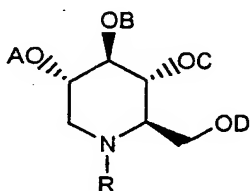
64. A pharmaceutical composition comprising a  
antiviral effective amount of the salt of claim 63.

65. A pharmaceutical composition comprising the salt of claim 63 further comprising a pharmaceutically acceptable carrier, diluent or excipient.

66. A method as set forth in claim 63 wherein R is selected from the group consisting of aryloxyalkyl, monohaloalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkenylcarbonyl, alkynylcarbonyl, 5 arylalkylcarbonyl, arylalkyloxycarbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl or R<sup>5</sup>.

67. A salt as set forth in claim 66 wherein when all of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> linkages are oxygen: (m + n + p) ≥ 2; and R<sup>1</sup> is not hydrogen or unsubstituted alkyl; or not all of any R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> groups are unsubstituted alkylene.

68. A pharmaceutical composition comprising N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof:



Formula I



5        wherein:

      R is aryloxyalkyl, monohaloalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, arylalkyloxycarbonyl, aryloxyalkylcarbonyl,

10    haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, perhaloalkylaralkyl or R<sup>5</sup>, wherein

$R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_pR^6-$ , wherein

      R<sup>1</sup> is alkyl, aryl, alkenyl, alkynyl, hydrogen or  
15    haloalkyl;

      R<sup>2</sup> is independently alkylene, alkenylene, alkynylene or haloalkylene;

      R<sup>3</sup> is independently alkylene, alkenylene, alkynylene or haloalkylene;

20        R<sup>4</sup> is independently alkylene, alkenylene, alkynylene or haloalkylene;

      R<sup>6</sup> is independently alkylene, alkenylene, alkynylene or haloalkylene;

      X<sup>1</sup> is independently oxygen, sulfur, sulfoxide or  
25    sulfone;

      X<sup>2</sup> is independently oxygen, sulfur, sulfoxide or sulfone;

      X<sup>3</sup> is independently oxygen, sulfur, sulfoxide or sulfone;

30        X<sup>4</sup> is independently oxygen, sulfur, sulfoxide or sulfone;

      m, n and p are independently 0, 1, 2, or 3;

      (m + n + p) ≤ 3; and

      (m + n + p) ≥ 1;

35        when all of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> linkages are oxygen;

140

(m + n + p)  $\geq$  2; and R<sup>1</sup> is not hydrogen or unsubstituted alkyl; or not all of any R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> groups are unsubstituted alkylene;

A, B, C, and D are independently hydrido, lower alkyl, 40 lowerhaloalkyl or acyl;

D and R taken together may form a five or six membered ring when R is carbonyl or alkylcarbonyl;

A and B taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

45 B and C taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

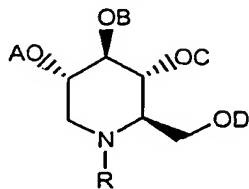
C and D taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

wherein the main chain in R contains between one and 50 twenty atoms;

the main chain of R<sup>5</sup> containing between four and twenty atoms; and

a pharmaceutically acceptable carrier, diluent, or excipient.

69. A method for treating a hepatitis virus infection in a mammal, comprising administering to said mammal a first amount of at least one substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically 5 acceptable salt thereof:



## Formula I

wherein:

R is alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, cycloalkenylalkyl, cycloalkenylalkenyl, cycloalkenylalkynyl, 10 bicycloalkenylalkyl, tricycloalkenylalkyl, tetracycloalkenylalkyl, bicycloalkenoxyalkyl, tricycloalkenoxyalkyl, tetracycloalkenyloxyalkyl, cycloalkylalkenyl, cycloalkylalkynyl, aralkenyl, aralkynyl, substituted aralkyl, aralkoxyalkyl, aralkoxyalkenyl, 15 aralkoxyalkynyl, aralkenoxyalkyl, aralkenoxyalkenyl, heteroarylalkyl, heterocyclooxyalkyl, heterocyclothiaalkyl, heterocycloalkenyl, heteroarylakenyl, heteroarylalkynyl, aryloxyalkyl, aryloxyalkenyl, aryloxyalkynyl, haloalkyl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkenyl, 20 dihydroxyalkenyl, hydroxyalkynyl, haloalkyloxyalkyl, haloalkoxyalkenyl, haloalkoxyalkynyl, carbonyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, arylcarbonylalkyl, arylalkylcarbonyl, arylalkenylcarbonyl, 25 arylalkyloxycarbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, alkyloxycarbonyl, alkanoyloxyalkyl, aryloxyalkoxyalkyl, aroyloxyalkyl, aminoalkyl, 30 alkanoylaminoalkyl, aminocarbonylalkyl, hydroxysulfonealkyl, aminosulfonealkyl, aminocarbonylaminoalkyl, aroylaminoalkyl, alkoxycarbonylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, perhaloalkylaralkyl or R<sup>5</sup>, wherein

R<sup>5</sup> = R<sup>1</sup>X<sup>1</sup>(R<sup>2</sup>X<sup>2</sup>)<sub>m</sub>(R<sup>3</sup>X<sup>3</sup>)<sub>n</sub>(R<sup>4</sup>X<sup>4</sup>)<sub>p</sub>R<sup>5</sup>-, wherein:

- 35         $R^1$  is alkyl, aryl, alkenyl, alkynyl, hydrogen or haloalkyl;
- $R^2$  is independently alkylene, alkenylene, alkynylene or haloalkylene;
- $R^3$  is independently alkylene, alkenylene, alkynylene or
- 40 haloalkylene;
- $R^4$  is independently alkylene, alkenylene, alkynylene or haloalkylene;
- $R^6$  is independently alkylene, alkenylene, alkynylene or haloalkylene;
- 45         $X^1$  is independently oxygen, sulfur, sulfoxide or sulfone;
- $X^2$  is independently oxygen, sulfur, sulfoxide or sulfone;
- $X^3$  is independently oxygen, sulfur, sulfoxide or
- 50 sulfone;
- $X^4$  is independently oxygen, sulfur, sulfoxide or sulfone;
- m, n and p are independently 0, 1, 2, or 3; and
- $m + n + p \leq 3$
- 55        A, B, C, and D are independently hydrido, lower alkyl, lowerhaloalkyl or acyl;
- D and R taken together may form a five or six membered ring when R is carbonyl or alkylcarbonyl;
- A and B taken together with the atoms to which they are
- 60 attached may form a five or six membered heterocyclic ring;
- B and C taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;
- C and D taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;
- 65        wherein the main chain in R contains between one and twenty atoms; and

the main chain of R<sup>5</sup> containing between four and twenty atoms; and

a second amount of an antiviral compound selected from  
70 the group consisting of a nucleoside antiviral compound, a  
nucleotide antiviral compound, an immunomodulator, an  
immunostimulant, and mixtures thereof,

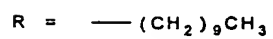
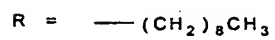
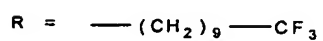
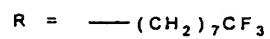
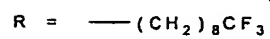
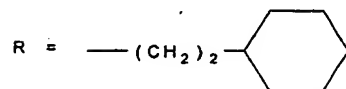
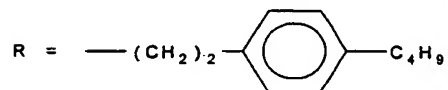
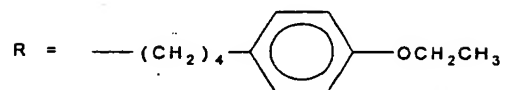
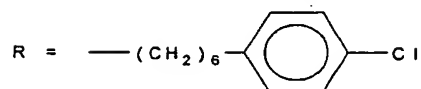
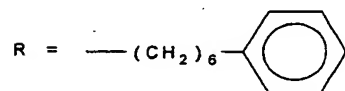
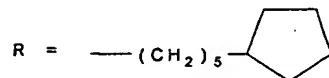
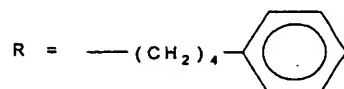
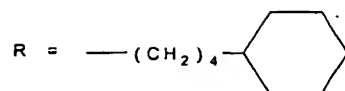
wherein said first and second amounts of said compounds  
together comprise an anti-hepatitis virus effective amount  
75 of said compounds.

70. A method as set forth in claim 69 wherein R is  
selected from the group consisting of aryloxyalkyl,  
monohaloalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl,  
cycloalkylalkyloxyalkyl, alkenylcarbonyl, alkynylcarbonyl,  
5 arylalkylcarbonyl, arylalkyloxycarbonyl,  
aryloxyalkylcarbonyl, haloalkylcarbonyl,  
hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl,  
cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl,  
perhaloalkylaralkyl or R<sup>5</sup>.

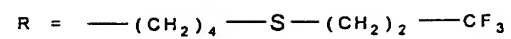
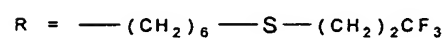
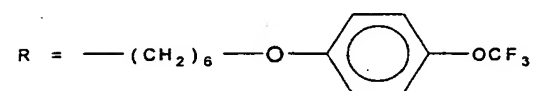
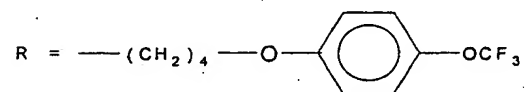
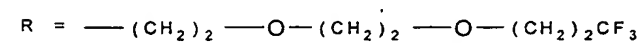
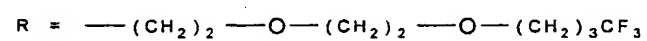
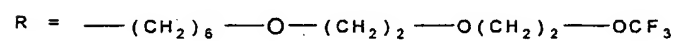
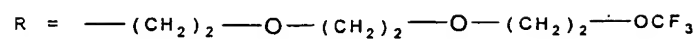
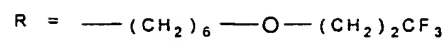
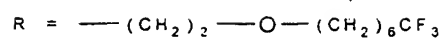
71. A method as set forth in claim 70 wherein when all  
of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> linkages are oxygen: (m + n + p) ≥  
2; and R<sup>1</sup> is not hydrogen or unsubstituted alkyl, or not all  
of any R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> groups are unsubstituted alkylene.

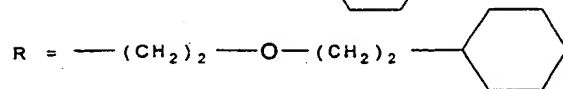
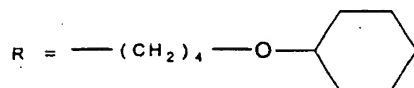
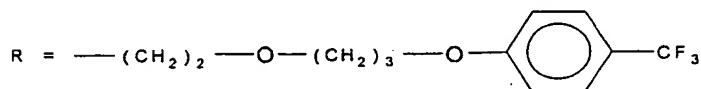
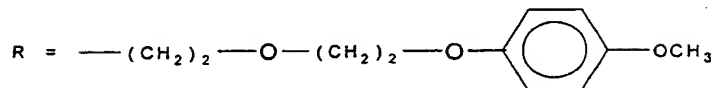
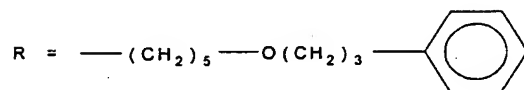
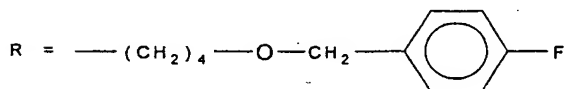
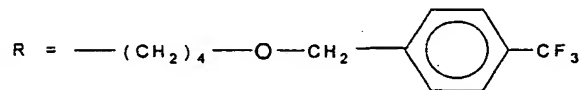
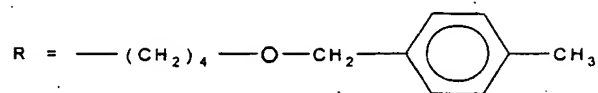
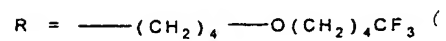
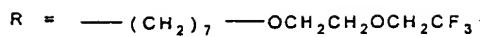
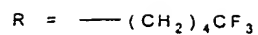
72. A method as set forth in claim 69 wherein said  
compound of Formula I wherein R is selected from the group  
consisting of:

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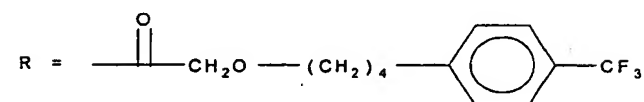
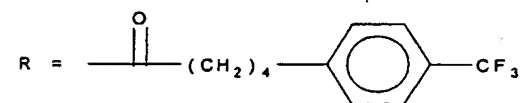
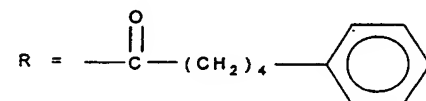
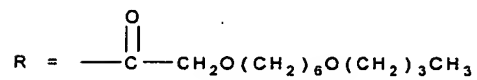
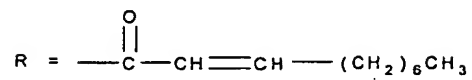
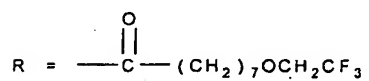
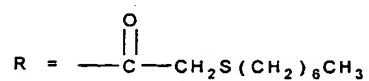
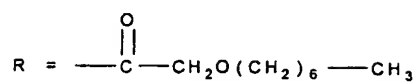
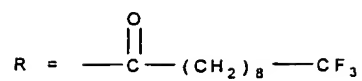
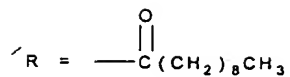
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73. A method as set forth in claim 69 wherein said nucleoside or nucleotide antiviral compound is selected from the group consisting of:

- (+)-cis-5-fluoro-1-[2-(hydroxy-methyl)-[1,3-oxathiolan-5-yl]cytosine;
- (-)-2'-deoxy-3'-thiacytidine-5'-triphosphate (3TC);
- (-)-cis-5-fluoro-1-[2-(hydroxy-methyl)-1,3-oxathiolan-5-yl]cytosine (FTC);
- (-)-2',3'-dideoxy-3'-thiacytidine [(-)-SddC];
- 10 1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)-5-iodocytosine (FIAC);
- 1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)-5-iodocytosine triphosphate (FIACTP);
- 1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)-5-methyluracil (FMAU);
- 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide;
- 2',3'-dideoxy-3'-fluoro-5-methyl-dexocytidine (FddMeCyt);
- 2',3'-dideoxy-3'-chloro-5-methyl-dexocytidine (ClddMeCyt);
- 20 2',3'-dideoxy-3'-amino-5-methyl-dexocytidine (AddMeCyt);
- 2',3'-dideoxy-3'-fluoro-5-methyl-cytidine (FddMeCyt);
- 2',3'-dideoxy-3'-chloro-5-methyl-cytidine (ClddMeCyt);
- 25 2',3'-dideoxy-3'-amino-5-methyl-cytidine (AddMeCyt);
- 2',3'-dideoxy-3'-fluorothymidine (FddThd);
- 2',3'-dideoxy-beta-L-5-fluorocytidine (beta-L-FddC);
- 2',3'-dideoxy-beta-L-5-thiacytidine;
- 2',3'-dideoxy-beta-L-5-cytidine (beta-L-ddC);
- 30 9-(1,3-dihydroxy-2-propoxymethyl)guanine;
- 2'-deoxy-3'-thia-5-fluorocytosine;
- 3'-amino-5-methyl-dexocytidine (AddMeCyt);

2-amino-1,9-[(2-hydroxymethyl-1-(hydroxymethyl)ethoxy)methyl]-6H-purin-6-one (gancyclovir);  
35 2-[2-(2-amino-9H-purin-9y)ethyl]-1,3-propandil diacetate (famciclovir);  
2-amino-1,9-dihydro-9-[(2-hydroxy-ethoxy)methyl]6H-purin-6-one (acyclovir);  
9-(4-hydroxy-3-hydroxymethyl-but-1-yl)guanine  
40 (penciclovir);  
9-(4-hydroxy-3-hydroxymethyl-but-1-yl)-6-deoxy-guanine, diacetate (famciclovir);  
3'-azido-3'-deoxythymidine (AZT);  
3'-chloro-5-methyl-dexocytidine (ClddMeCyt);  
45 9-(2-phosphonyl-methoxyethyl)-2',6'-diaminopurine-2',3'-dideoxyriboside;  
9-(2-phosphonylmethoxyethyl)adenine (PMEA);  
acyclovir triphosphate (ACVTP);  
D-carbocyclic-2'-deoxyguanosine (CdG);  
50 dideoxy-cytidine;  
dideoxy-cytosine (ddC);  
dideoxy-guanine (ddG);  
dideoxy-inosine (ddI);  
E-5-(2-bromovinyl)-2'-deoxyuridine triphosphate;  
55 fluoro-arabinofuranosyl-iodouracil;  
1-(2'-deoxy-2'-fluoro-1-beta-D-arabinofuranosyl)-5-iodo-uracil (FIAU);  
stavudine;  
9-beta-D-arabinofuranosyl-9H-purine-6-amine monohydrate  
60 (Ara-A);  
9-beta-D-arabinofuranosyl-9H-purine-6-amine-5'-monophosphate monohydrate (Ara-AMP);  
2-deoxy-3'-thia-5-fluorocytidine;  
2',3'-dideoxy-guanine; and  
65 2',3'-dideoxy-guanosine.

74. A method as set forth in claim 69 comprising administering to said mammal from about 0.1 mg/kg/day to about 100 mg/kg/day of at least one N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a  
5 pharmaceutically acceptable salt thereof; and

from about 0.1 mg/person/day to about 500 mg/person/day of a compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and a mixture thereof.

75. A method as set forth in claim 74 comprising administering between about 0.1 mg/person/day and about 500 mg/person/day of (-)-2'-deoxy-3'-thiocytidine-5'-triphosphate.

76. A method as set forth in claim 69 comprising treating a hepatitis B virus infection comprising administering to said mammal an anti-hepatitis B virus effective amount of at least one  
5 N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof.

77. A method as set forth in claim 68 comprising treating a hepatitis C virus infection comprising administering to said mammal an anti-hepatitis C virus effective amount of at least one  
5 N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof.

78. A method as set forth in claim 68 wherein R is alkenyl, alkynyl, substituted arylalkyl, aryloxyalkyl, haloalkyl, hydroxyalkyl, haloalkyloxyalkyl, carbonyl,

cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkylcarbonyl,  
5 alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl,  
arylalkyloxyalkylcarbonyl, aryloxyalkylcarbonyl,  
haloalkylcarbonyl, hydroxyalkylcarbonyl,  
haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl,  
alkoxyalkylcarbonyl, alkyloxyalkylcarbonyl, perhaloalkylaralkyl  
10 or  $R^5$ , wherein

$$R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_pR^6-$$

$R^1$  is alkyl, aryl, alkenyl, alkynyl, hydrogen or  
haloalkyl;

$R^2$  is independently alkylene, alkenylene, alkynylene or  
15 haloalkylene;

$R^3$  is independently alkylene, alkenylene, alkynylene or  
haloalkylene;

$R^4$  is independently alkylene, alkenylene, alkynylene or  
haloalkylene;

20  $R^6$  is independently alkylene, alkenylene, alkynylene or  
haloalkylene;

$X^1$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

$X^2$  is independently oxygen, sulfur, sulfoxide or  
25 sulfone;

$X^3$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

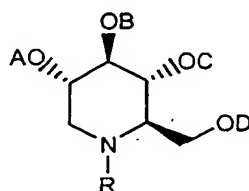
$X^4$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

30  $m$ ,  $n$  and  $p$  are independently 0, 1, 2, or 3; and  
 $m + n + p \leq 3$ ,

wherein the main chain in  $R$  contains between one and  
twenty atoms;

the main chain of  $R^5$  containing between four and twenty  
35 atoms.

79. A pharmaceutical composition comprising an anti-hepatitis effective amount of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof:



40

Formula I

wherein:

R is alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, cycloalkenylalkyl, cycloalkenylalkenyl, cycloalkenylalkynyl, bicycloalkenylalkyl, tricycloalkenylalkyl,  
 45 tetracycloalkenylalkyl, bicycloalkenoxyalkyl, tricycloalkenoxyalkyl, tetracycloalkenyloxyalkyl, cycloalkylalkenyl, cycloalkylalkynyl, aralkenyl, aralkynyl, substituted aralkyl, aralkoxyalkyl, aralkoxyalkenyl, aralkoxyalkynyl, aralkenoxyalkyl, aralkenoxyalkenyl,  
 50 heteroarylalkyl, heterocyclooxyalkyl, heterocyclothiaalkyl, heterocycloalkenyl, heteroarylakenyl, heteroarylalkynyl, aryloxyalkyl, aryloxyalkenyl, aryloxyalkynyl, haloalkyl, hydroxyalkyl; dihydroxyalkyl, hydroxyalkenyl, dihydroxyalkenyl, hydroxyalkynyl, haloalkyloxyalkyl,  
 55 haloalkoxyalkenyl, haloalkoxyalkynyl, carbonyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, arylcarbonylalkyl,

arylalkylcarbonyl, arylalkenylcarbonyl,  
 arylalkyloxycarbonyl, aryloxyalkylcarbonyl,  
 60 haloalkylcarbonyl, hydroxyalkylcarbonyl,  
 haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl,  
 alkoxyalkylcarbonyl, alkyloxycarbonyl, alkanoyloxyalkyl,  
 aryloxyalkoxyalkyl, aroyloxyalkyl, aminoalkyl, amino(alkyl),  
 alkanoylaminoalkyl, aminocarbonylalkyl, hydroxysulfonealkyl,  
 65 aminosulfonealkyl, aminocarbonylaminoalkyl,  
 aroylaminoalkyl, alkoxycarbonylaminoalkyl, carboxyalkyl,  
 alkoxycarbonylalkyl, perhaloalkylaralkyl or  $R^5$ , wherein

$R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_pR^6-$ , wherein:

$R^1$  is alkyl, aryl, alkenyl, alkynyl, hydrogen or  
 70 haloalkyl;

$R^2$  is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;

$R^3$  is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;

75  $R^4$  is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;

$R^6$  is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;

$X^1$  is independently oxygen, sulfur, sulfoxide or  
 80 sulfone;

$X^2$  is independently oxygen, sulfur, sulfoxide or  
 sulfone;

$X^3$  is independently oxygen, sulfur, sulfoxide or  
 sulfone;

85  $X^4$  is independently oxygen, sulfur, sulfoxide or  
 sulfone;

$m$ ,  $n$  and  $p$  are independently 0, 1, 2, or 3; and

$m + n + p \leq 3$

A, B, C, and D are independently hydrido, lower alkyl,  
 90 lowerhaloalkyl or acyl;

D and R taken together may form a five or six membered ring when R is carbonyl or alkylcarbonyl;

A and B taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

95 B and C taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring; and

C and D taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

100 wherein the main chain in R contains between one and twenty atoms; and

the main chain of R<sup>5</sup> containing between four and twenty atoms; and

a pharmaceutically acceptable carrier, diluent or  
105 excipient.

80. A pharmaceutical composition as set forth in claim 79 wherein R is selected from the group consisting of aryloxyalkyl, monohaloalkyl, haloalkyloxyalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl,  
5 alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, arylalkyloxycarbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, perhaloalkylaralkyl or R<sup>5</sup>.

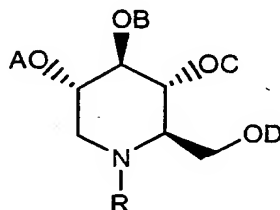
81. A pharmaceutical composition as set forth in claim 80 wherein when all of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> linkages are oxygen: (m + n + p) ≥ 2; and R<sup>1</sup> is not hydrogen or unsubstituted alkyl, or not all of any R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> groups are unsubstituted alkylene.



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82. A pharmaceutical composition as set forth in claim 79 wherein R is alkenyl, alkynyl, substituted arylalkyl, aryloxyalkyl, haloalkyl, hydroxyalkyl, haloalkyloxyalkyl, carbonyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, arylalkyloxy carbonyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, alkyloxy carbonyl or R<sup>5</sup>.

83. An N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof:



Formula I

10 wherein R is selected from the group consisting of alkenylcarbonyl, alkynylcarbonyl, arylalkylcarbonyl, aryloxyalkyl, aryloxyalkylcarbonyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl, cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl, 15 cycloalkylalkylcarbonyl, alkoxy carbonyl, alkylcarbonyl, aryloxyalkoxyalkylcarbonyl, alkylcarbonyloxyalkylcarbonyl, arylcarbonyloxyalkylcarbonyl, aminoalkylcarbonyl,

alkylcarbonylaminoalkylcarbonyl,  
arylcarbonylaminoalkylcarbonyl,  
20 alkoxycarbonylaminoalkylcarbonyl,  
aminocarbonylaminoalkylcarbonyl,  
aminothiocarbonylaminoalkylcarbonyl, arylalkenylcarbonyl,  
carboxyalkylcarbonyl, alkoxycarbonylalkylcarbonyl,  
aminocarbonylalkylcarbonyl, aminothiocarbonylalkylcarbonyl,  
25 aminosulfonealkylcarbonyl, arylalkynylcarbonyl,  
heterocycloalkylcarbonyl, heteroarylalkylcarbonyl,  
heteroaryloxyalkylcarbonyl, heteroarylthiaalkylcarbonyl,  
heterocyclooxyalkylcarbonyl, heterocyclothiaalkylcarbonyl,  
arylthiaalkylcarbonyl, monohaloalkylcarbonyl,  
30 haloalkyloxyalkylcarbonyl, cycloalkylalkyloxyalkylcarbonyl  
or R<sup>5</sup>carbonyl wherein:

$R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_pR^6$ - wherein

R<sup>1</sup> is alkyl, aryl, alkenyl, alkynyl, hydrogen or  
haloalkyl;

35 R<sup>2</sup> is independently alkylene, alkenylene, alkynylene or  
haloalkylene;

R<sup>3</sup> is independently alkylene, alkenylene, alkynylene or  
haloalkylene;

R<sup>4</sup> is independently alkylene, alkenylene, alkynylene or  
40 haloalkylene;

R<sup>6</sup> is independently alkylene, alkenylene, alkynylene or  
haloalkylene;

X<sup>1</sup> is independently oxygen, sulfur, sulfoxide or  
sulfone;

45 X<sup>2</sup> is independently oxygen, sulfur, sulfoxide or  
sulfone;

X<sup>3</sup> is independently oxygen, sulfur, sulfoxide or  
sulfone;

X<sup>4</sup> is independently oxygen, sulfur, sulfoxide or  
50 sulfone;

m, n and p are independently 0, 1, 2, or 3;

$(m + n + p) \leq 3$ ;

$(m + n + p) \geq 1$ ;

when all of any  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  linkages are oxygen;

55  $(m + n + p) \geq 2$ ; and  $R^1$  is not hydrogen or

unsubstituted alkyl; or not all of any  $R^2$ ,  $R^3$  and  $R^4$  groups are unsubstituted alkylene;

A, B, C, and D are independently hydrido, lower alkyl, lowerhaloalkyl or acyl;

60 D and R taken together may form a five or six membered ring when R is carbonyl or alkylcarbonyl;

A and B taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

B and C taken together with the atoms to which they are  
65 attached may form a five or six membered heterocyclic ring;

C and D taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

wherein the main chain in R contains between one and twenty atoms;

70 the main chain of  $R^5$  containing between four and twenty atoms;

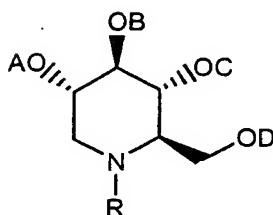
when all of any  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  linkages are oxygen; and

$(m + n + p) \geq 2$ ; and  $R^1$  is not hydrogen or  
75 unsubstituted alkyl; or not all of any  $R^2$ ,  $R^3$  and  $R^4$  groups are unsubstituted alkylene.

84. A pharmaceutical composition comprising an antiviral amount of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound as set forth in claim 83 and a pharmaceutically acceptable carrier, diluent or excipient.

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85. An N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof:



5

Formula I

wherein R is selected from the group consisting of  
 aryloxyalkylcarbonyl, haloalkylcarbonyl,  
 hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl,  
 cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl,  
 10 cycloalkylalkylcarbonyl, aryloxyalkoxyalkylcarbonyl,  
 arylcarbonyloxyalkylcarbonyl, aminoalkylcarbonyl,  
 alkylcarbonylaminoalkylcarbonyl,  
 arylcarbonylaminoalkylcarbonyl,  
 alkoxycarbonylaminoalkylcarbonyl,  
 15 aminocarbonylaminoalkylcarbonyl,  
 aminothiocabonylaminoalkylcarbonyl, carboxyalkylcarbonyl,  
 alkoxycarbonylalkylcarbonyl, aminocarbonylalkylcarbonyl,  
 aminothiocabonylalkylcarbonyl, aminosulfonealkylcarbonyl,  
 arylalkynylcarbonyl, heterocycloalkylcarbonyl,  
 20 heteroarylalkylcarbonyl, heteroaryloxyalkylcarbonyl,  
 heteroarylthiaalkylcarbonyl, heterocyclooxyalkylcarbonyl,  
 heterocyclothiaalkylcarbonyl, arylthiaalkylcarbonyl,  
 monohaloalkylcarbonyl, haloalkyloxyalkylcarbonyl,  
 cycloalkylalkyloxyalkylcarbonyl, or R<sup>5</sup>carbonyl wherein

- 25  $R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_pR^6$ - wherein  
     $R^1$  is alkyl, aryl, alkenyl, alkynyl, hydrogen or  
    haloalkyl;  
     $R^2$  is independently alkylene, alkenylene, alkynylene or  
    haloalkylene;  
30  $R^3$  is independently alkylene, alkenylene, alkynylene or  
    haloalkylene;  
     $R^4$  is independently alkylene, alkenylene, alkynylene or  
    haloalkylene;  
     $R^6$  is independently alkylene, alkenylene, alkynylene or  
35 haloalkylene;  
     $X^1$  is independently oxygen, sulfur, sulfoxide or  
    sulfone;  
     $X^2$  is independently oxygen, sulfur, sulfoxide or  
    sulfone;  
40  $X^3$  is independently oxygen, sulfur, sulfoxide or  
    sulfone;  
     $X^4$  is independently oxygen, sulfur, sulfoxide or  
    sulfone;  
    m, n and p are independently 0, 1, 2, or 3;  
45  $(m + n + p) \leq 3$ ;  
     $(m + n + p) \geq 1$ ;  
    when all of any  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  linkages are oxygen;  
     $(m + n + p) \geq 2$ ; and  $R^1$  is not hydrogen or  
    unsubstituted alkyl; or not all of any  $R^2$ ,  $R^3$  and  $R^4$  groups  
50 are unsubstituted alkylene;  
    A, B, C, and D are independently hydrido, lower alkyl,  
    lowerhaloalkyl or acyl;  
    D and R taken together may form a five or six membered  
    ring when R is carbonyl or alkylcarbonyl;  
55 A and B taken together with the atoms to which they are  
    attached may form a five or six membered heterocyclic ring;

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B and C taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

C and D taken together with the atoms to which they are  
 60 attached may form a five or six membered heterocyclic ring;  
 wherein the main chain in R contains between one and  
 twenty atoms;

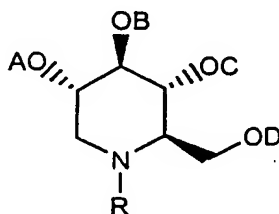
the main chain of R<sup>5</sup> containing between four and twenty  
 atoms;

65 when all of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> linkages are oxygen;  
 and

(m + n + p) ≥ 2; and R<sup>1</sup> is not hydrogen or  
 unsubstituted alkyl; or not all of any R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> groups  
 are unsubstituted alkylene.

86. A pharmaceutical composition comprising an  
 antiviral amount of an N-substituted-1,5-dideoxy-1,5-imino-  
 D-glucitol compound as set forth in claim I and a  
 pharmaceutically acceptable carrier, diluent or excipient.

87. An N-substituted-1,5-dideoxy-1,5-imino-D-glucitol  
 compound of Formula I or a pharmaceutically acceptable salt  
 thereof:



- wherein R is selected from the group consisting of  
 aryloxyalkylcarbonyl, haloalkylcarbonyl,  
 hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl,  
 cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl,  
 10 cycloalkylalkylcarbonyl, aryloxyalkoxyalkylcarbonyl,  
 arylcarbonyloxyalkylcarbonyl, aminoalkylcarbonyl,  
 alkylcarbonylaminoalkylcarbonyl,  
 arylcarbonylaminoalkylcarbonyl,  
 alkoxycarbonylaminoalkylcarbonyl,  
 15 aminocarbonylaminoalkylcarbonyl,  
 aminothiocabonylaminoalkylcarbonyl, carboxyalkylcarbonyl,  
 alkoxycarbonylalkylcarbonyl, aminocarbonylalkylcarbonyl,  
 aminothiocabonylalkylcarbonyl, aminosulfonealkylcarbonyl,  
 arylalkynylcarbonyl, heterocycloalkylcarbonyl,  
 20 heteroarylalkylcarbonyl, heteroaryloxyalkylcarbonyl,  
 heteroarylthiavcarbonyl, heterocyclooxyalkylcarbonyl,  
 heterocyclothiaalkylcarbonyl, arylthiaalkylcarbonyl,  
 monohaloalkylcarbonyl, haloalkyloxyalkylcarbonyl or  
 cycloalkylalkyloxyalkylcarbonyl wherein  
 25  $R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_pR^6-$  wherein  
 $R^1$  is alkyl, aryl, alkenyl, alkynyl, hydrogen or  
 haloalkyl;  
 $R^2$  is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;  
 30  $R^3$  is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;  
 $R^4$  is independently alkylene, alkenylene, alkynylene or  
 haloalkylene;  
 $R^6$  is independently alkylene, alkenylene, alkynylene or  
 35 haloalkylene;  
 $X^1$  is independently oxygen, sulfur, sulfoxide or  
 sulfone;

$X^2$  is independently oxygen, sulfur, sulfoxide or sulfone;

40  $X^3$  is independently oxygen, sulfur, sulfoxide or sulfone;

$X^4$  is independently oxygen, sulfur, sulfoxide or sulfone;

$m$ ,  $n$  and  $p$  are independently 0, 1, 2, or 3;

45  $(m + n + p) \leq 3$ ;

$(m + n + p) \geq 1$ ;

when all of any  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  linkages are oxygen;

$(m + n + p) \geq 2$ ; and  $R^1$  is not hydrogen or unsubstituted alkyl; or not all of any  $R^2$ ,  $R^3$  and  $R^4$  groups  
50 are unsubstituted alkylene;

$A$ ,  $B$ ,  $C$ , and  $D$  are independently hydrido, lower alkyl, lowerhaloalkyl or acyl;

$D$  and  $R$  taken together may form a five or six membered ring when  $R$  is carbonyl or alkylcarbonyl;

55  $A$  and  $B$  taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

$B$  and  $C$  taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

$C$  and  $D$  taken together with the atoms to which they are  
60 attached may form a five or six membered heterocyclic ring;

wherein the main chain in  $R$  contains between one and twenty atoms;

the main chain of  $R^5$  containing between four and twenty atoms;

65 when all of any  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  linkages are oxygen; and

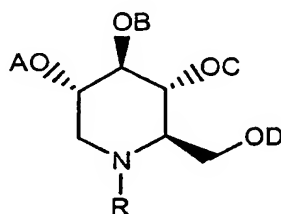
$(m + n + p) \geq 2$ ; and  $R^1$  is not hydrogen or unsubstituted alkyl; or not all of any  $R^2$ ,  $R^3$  and  $R^4$  groups are unsubstituted alkylene.



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88. A pharmaceutical composition comprising an antiviral amount of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound as set forth in claim 87 and a pharmaceutically acceptable carrier, diluent or excipient.

89. An N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof:



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Formula I

wherein R is selected from the group consisting of:

aryloxyalkylcarbonyl, haloalkylcarbonyl,  
hydroxyalkylcarbonyl, haloalkyloxyalkylcarbonyl,  
cycloalkyloxyalkylcarbonyl, alkoxyalkylcarbonyl,  
10 cycloalkylalkylcarbonyl, aryloxyalkoxyalkylcarbonyl,  
arylcarbonyloxyalkylcarbonyl, aminoalkylcarbonyl,  
alkylcarbonylaminoalkylcarbonyl,  
arylcarbonylaminoalkylcarbonyl,  
alkoxycarbonylaminoalkylcarbonyl,  
15 aminocarbonylaminoalkylcarbonyl,  
aminothiocarbonylaminoalkylcarbonyl, carboxyalkylcarbonyl,  
alkoxycarbonylalkylcarbonyl, aminocarbonylalkylcarbonyl,  
aminothiocarbonylalkylcarbonyl, aminosulfonealkylcarbonyl,  
arylalkynylcarbonyl, heterocycloalkylcarbonyl,

20 heteroarylalkylcarbonyl, heteroaryloxyalkylcarbonyl,  
heteroarylthiaalkylcarbonyl, heterocyclooxyalkylcarbonyl,  
heterocyclothiaalkylcarbonyl, arylthiaalkylcarbonyl,  
monohaloalkylcarbonyl, haloalkyloxyalkylcarbonyl,  
cycloalkylalkyloxyalkylcarbonyl, or  $R^5$ carbonyl wherein

25  $R^5 = R^1X^1(R^2X^2)_m(R^3X^3)_n(R^4X^4)_pR^6$ - wherein

$R^1$  is alkyl, aryl, alkenyl, alkynyl, hydrogen or  
haloalkyl;

$R^2$  is independently alkylene, alkenylene, alkynylene or  
haloalkylene;

30  $R^3$  is independently alkylene, alkenylene, alkynylene or  
haloalkylene;

$R^4$  is independently alkylene, alkenylene, alkynylene or  
haloalkylene;

$R^6$  is independently alkylene, alkenylene, alkynylene or  
35 haloalkylene;

$X^1$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

$X^2$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

40  $X^3$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

$X^4$  is independently oxygen, sulfur, sulfoxide or  
sulfone;

$m$ ,  $n$  and  $p$  are independently 0, 1, 2, or 3;

45  $(m + n + p) \leq 3$ ;

$(m + n + p) \geq 1$ ;

when all of any  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  linkages are oxygen;

$(m + n + p) \geq 2$ ; and  $R^1$  is not hydrogen or  
unsubstituted alkyl; or not all of any  $R^2$ ,  $R^3$  and  $R^4$  groups  
50 are unsubstituted alkylene;

$A$ ,  $B$ ,  $C$ , and  $D$  are independently hydrido, lower alkyl,  
lowerhaloalkyl or acyl;

D and R taken together may form a five or six membered ring when R is carbonyl or alkylcarbonyl;

55 A and B taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

B and C taken together with the atoms to which they are attached may form a five or six membered heterocyclic ring;

C and D taken together with the atoms to which they are  
60 attached may form a five or six membered heterocyclic ring;

wherein the main chain in R contains between one and twenty atoms;

the main chain of R<sup>5</sup> containing between four and twenty atoms;

65 when all of any X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> linkages are oxygen;  
and

(m + n + p) ≥ 2; and R<sup>1</sup> is not hydrogen or unsubstituted alkyl; or not all of any R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> groups are unsubstituted alkylene.

90. A pharmaceutical composition comprising an antiviral amount of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound as set forth in claim 89 and a pharmaceutically acceptable carrier, diluent or excipient.

FIG. 1

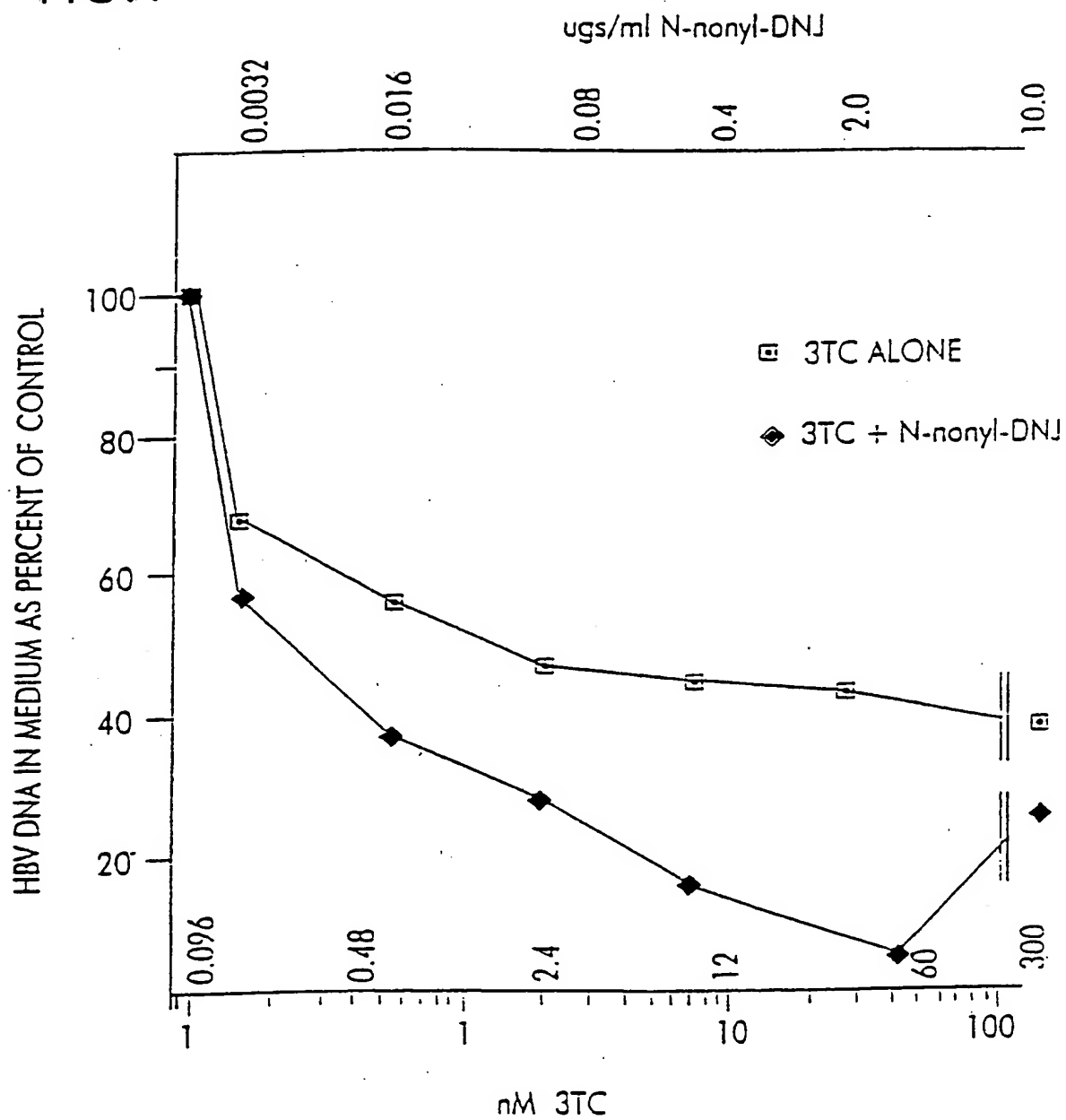


FIG. 2

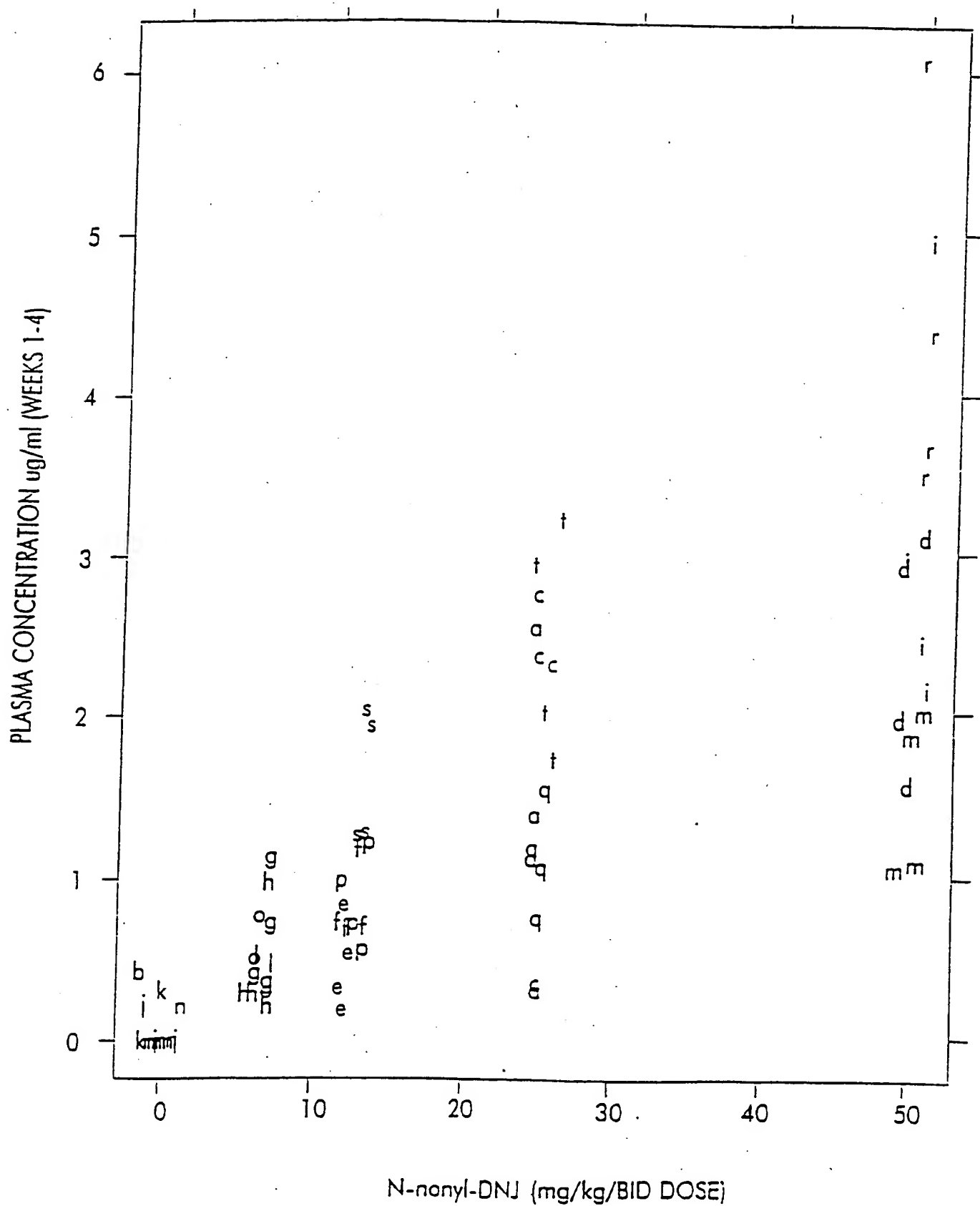
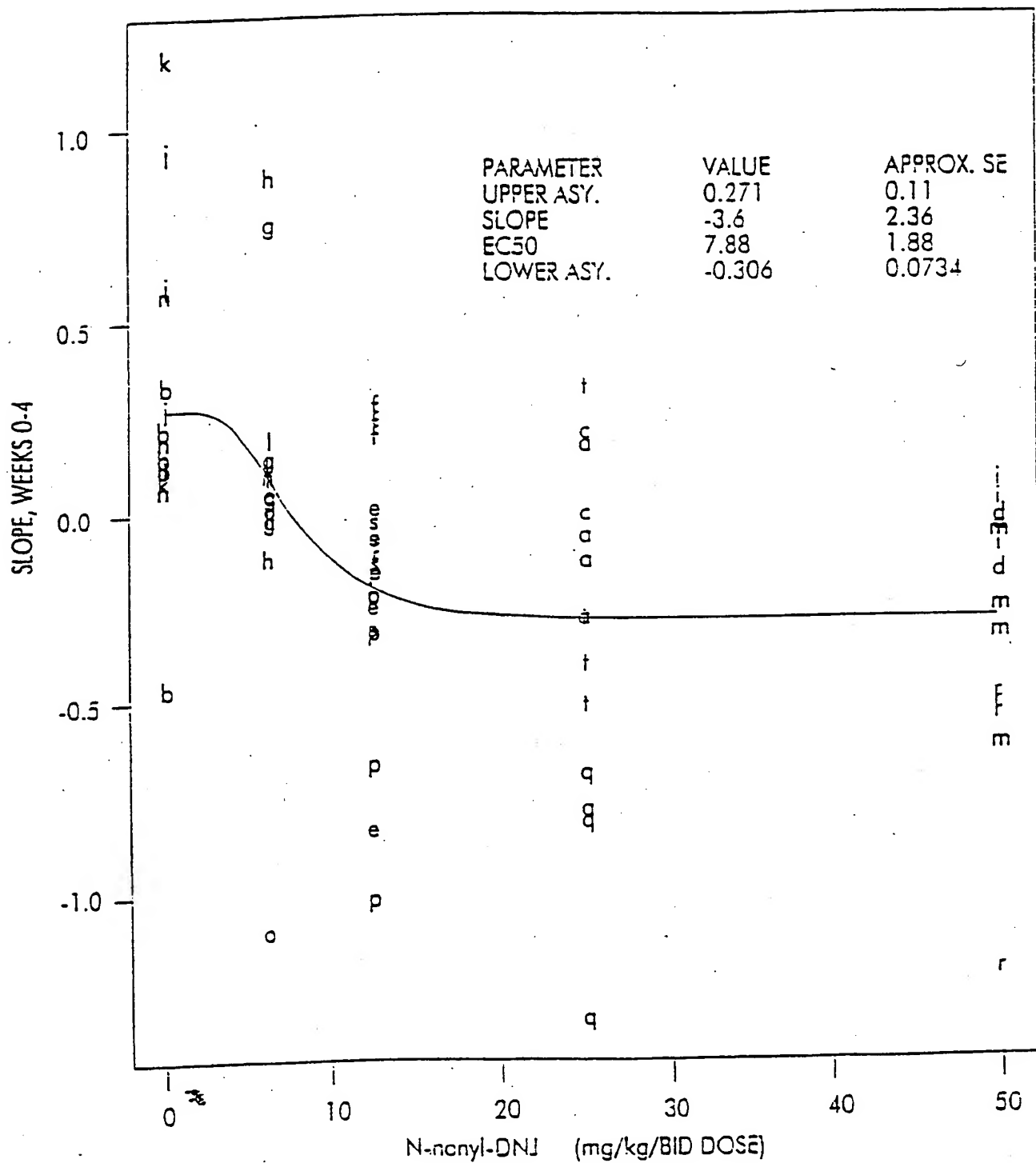


FIG.3



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(74) Agents: **ROEDEL, John, K., Jr.**; Senniger, Powers,  
Leavitt & Roedel, One Metropolitan Square, 16th floor,  
St. Louis, MO 63102 et al. (US).

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LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,  
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(71) Applicant (*for all designated States except US*): **G.D.  
SEARLE & CO.** [US/US]; Corporate Patent Dept., P.O.  
Box 5110, Chicago, IL 60680-5110 (US).

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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **MUELLER,**  
**Richard, A.** [US/US]; 562 Stonegate Terrace, Glencoe, IL  
60022 (US). **BRYANT, Martin, L.** [US/US]; 65 Hickory  
Lane, Carlisle, MA 01741 (US). **PARTIS, Richard, A.**  
[US/US]; 2221 Noyes Street, Evanston, IL 60201 (US).

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*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
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**WO 00/47198 A3**

(54) Title: **USE OF SUBSTITUTED-1,5-DIDEOXY-1,5-IMINO-D-GLUCITOL COMPOUNDS FOR TREATING HEPATITIS  
VIRUS INFECTIONS**

(57) Abstract: N-Substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds of Formula (I) are effective in treatment of hepatitis  
infections, including hepatitis B and hepatitis C. In treating hepatitis infections, the compounds of Formula (I) may be used alone, or  
in combination with another antiviral agent selected from among nucleosides, nucleotides, immunomodulators, immunostimulants  
or various combinations of such other agents.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/03768A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K31/445 A61P31/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; May 1998 (1998-05) BLOCK TIMOTHY M ET AL: "Treatment of chronic hepatitis virus infection in a woodchuck animal model with an inhibitor of protein folding and trafficking." Database accession no. PREV199800265466 XP002152104 abstract & NATURE MEDICINE, vol. 4, no. 5, May 1998 (1998-05), pages 610-614, ISSN: 1078-8956 — —/—	1-90

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Orviz Diaz, P



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/03768

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BLOCK T M ET AL: "SECRETION OF HUMAN HEPATITIS B VIRUS IS INHIBITED BY THE IMINO SUGAR N-BUTYLDEOXYNOJIRIMYCIN" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 91, no. 6, March 1994 (1994-03), pages 2235-2239, XP000952542 ISSN: 0027-8424 cited in the application the whole document	1-90
P, X	ZITZMANN N ET AL: "IMINO SUGARS INHIBIT THE FORMATION AND SECRETION OF BOVINE VIRAL DIARRHEA VIRUS, A PESTIVIRUS MODEL OF HEPATITIS C VIRUS: IMPLICATIONS FOR THE DEVELOPMENT OF BROAD SPECTRUM ANTI-HEPATITIS VIRUS AGENTS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 96, no. 21, 1999, pages 11878-11882, XP000952534 ISSN: 0027-8424 the whole document	1-90
X	PLATT F M ET AL: "N-BUTYLDEOXYNOJIRIMYCIN IS A NOVEL INHIBITOR OF GLYCOLIPID BIOSYNTHESIS. SECRETION OF HUMAN HEPATITIS B VIRUS IS INHIBITED BY THE IMINO SUGAR N-BUTYLDEOXYNOJIRIMYCIN" CHEMTRACTS ORGANIC CHEMISTRY, US, DATA TRACE CHEMISTRY PUBLISHERS, 1994, pages 106-107, XP002067581 ISSN: 0895-4445 the whole document	1-90
X	WO 95 19172 A (SEARLE & CO ; MONSANTO CO (US); BLOCK TIMOTHY M (US); BLUMBERG BARU) 20 July 1995 (1995-07-20) the whole document	1-90
X	WO 98 35685 A (DWEK RAYMOND A ; SEARLE & CO (US); BLOCK TIMOTHY M (US); JACOB GARY) 20 August 1998 (1998-08-20) the whole document	1-90
P, X	WO 99 29321 A (ZITZMANN NICOLE ; PLATT FRANCES (GB); UNIV OXFORD (GB); BUTTERS TER) 17 June 1999 (1999-06-17) the whole document	1-90
	-/-	

# INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/US 00/03768

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 40916 A (MUELLER RICHARD A ; SEARLE & CO (US); BRYANT MARTIN L (US); PARTIS) 19 August 1999 (1999-08-19) the whole document	1-90
A	US 4 611 058 A (KOEERNICK WOLFGANG) 9 September 1986 (1986-09-09) the whole document	1-90
A	WO 91 17145 A (SEARLE & CO) 14 November 1991 (1991-11-14) the whole document	1-90

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

In view of the extremely large number of claims and of the overlapping subject-matter of some claims a complete search was not possible (Art. 6 PCT). The search had to be limited to the general concept (use of N-substituted derivatives of 1,5-dideoxy-1,5-imino-D-glucitol) and more specifically to the specific compounds mentioned in tables 2 and 3 of the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/US 00/03768

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9519172 A	20-07-1995	AT 186836 T	15-12-1999
		AU 1403795 A	01-08-1995
		CA 2181033 A	20-07-1995
		CN 1149253 A	07-05-1997
		DE 69421828 D	30-12-1999
		DE 69421828 T	20-04-2000
		EP 0739205 A	30-10-1996
		ES 2140652 T	01-03-2000
		GR 3032527 T	31-05-2000
		JP 9508111 T	19-08-1997
		PT 739205 T	28-04-2000
		US 6037351 A	14-03-2000
WO 9835685 A	20-08-1998	AU 6169298 A	08-09-1998
		CN 1251993 T	03-05-2000
		EP 1007058 A	14-06-2000
WO 9929321 A	17-06-1999	AU 1721599 A	28-06-1999
		BR 9813508 A	03-10-2000
		EP 1037636 A	27-09-2000
WO 9940916 A	19-08-1999	AU 2759599 A	30-08-1999
		BR 9907882 A	17-10-2000
US 4611058 A	09-09-1986	DE 3049446 A	29-07-1982
		AT 7138 T	15-05-1984
		DE 3163240 D	24-05-1984
		EP 0055431 A	07-07-1982
		JP 1626145 C	28-11-1991
		JP 2045624 B	11-10-1990
		JP 57134465 A	19-08-1982
WO 9117145 A	14-11-1991	US 5151519 A	29-09-1992
		AU 7984491 A	27-11-1991
		PT 97592 A	28-02-1992
		US 5281724 A	25-01-1994
		ZA 9103445 A	29-07-1992